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(54) Title: 45 HUMAN SECRETED PROTEINS			
(57) Abstract The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.			

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45 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and
5 their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum
15 (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or
20 secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include
30 the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using
35 secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron. In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence

of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress

background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or

without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods.

Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

The translation product of this gene shares sequence homology with tapasin and poliovirus receptor, which are thought to be important in the assembly and function of

multimeric MHC class I-TAP complexes or poliovirus infection. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: VKVKEKSAAEGTGKKPKGCR L PGVLGEPPSSAGPRKQRRTVEKGG GQGGNSRAAS (SEQ ID NO:109). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in early stage human liver, placental tissues, a breast cancer cell line treated with 0.3 nM R1881 compound as well as breast tissue, and to a lesser extent in many other tissues in an ubiquitous manner.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, reproductive, and hepatic disorders and diseases, and infection, e.g., enteroviral (poliovirus or other picornaviruses), and proper placental function. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and placenta, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, placental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:60 as residues: Ala-19 to Gln-29.

The tissue distribution in human liver, combined with the homology to tapasin, poliovirus receptor, and other immunoglobulin molecules indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or intervention of immune related disorders or viral infections. The utility includes immune modulation, tissue/organ transplantation, tumor immunity, allergy treatment, and autoimmune diseases.

Expression within embryonic (placental) tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in

cancer therapy. Furthermore, the tissue distribution in breast cancer tissue indicates that the translation product of this gene is useful for the diagnosis and/or treatment of breast cancers, as well as cancers of other tissues where expression has been observed.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1796 of SEQ ID NO:11, b is an integer of 15 to 1810, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

The translation product of this gene shares sequence homology with lysyl hydroxylase, which is thought to be important in the post-translational biosynthesis of collagen; specifically, the formation of hydroxylysine in collagens. When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells, and to a lesser extent other musculo-skeletal cells, through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in placental and breast tissues, as well as a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, osteogenesis imperfecta, chondrodysplasias, osteoporosis, osteoarthritis, Alport syndrome, Ehlers-Danlos syndrome as well as other connective tissue disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell

type(s). For a number of disorders of the above tissues or cells, particularly of the connective tissue, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., connective, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in placenta and the homology to lysyl hydroxylase, in conjunction with the biological activity data, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of conditions related to vascular or reproductive disorders, and potentially in the biosynthesis of collagen. The collagen superfamily of proteins now contains at least 19 proteins formally defined as collagens and an additional ten proteins that have collagen-like domains.

The most abundant collagens form extracellular fibrils or network-like structures, but the others fulfill a variety of biological functions. There are at least eight highly specific post-translational enzymes involved in collagen biosynthesis. The protein product of this gene is quite likely another. Over 400 mutations in 6 different collagens cause a variety of human diseases that include osteogenesis imperfecta, chondrodysplasias, some forms of osteoporosis, some forms of osteoarthritis, and the renal disease known as the Alport syndrome. Many of the disease phenotypes have been produced in transgenic mice with mutated collagen genes. There has been increasing interest in the possibility that the unique post-translational enzymes involved in collagen biosynthesis, such as the protein product of this gene, offer attractive targets for specifically inhibiting excessive fibrotic reactions in a number of diseases.

Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, and/or atherosclerosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2339 of SEQ ID NO:12, b is an integer of 15 to 2353, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The translation product of this gene shares sequence homology with a murine G-protein coupled receptor, which is thought to be important in signal transduction for extracellular signals (See Genbank Accession No.: AF027955). In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: EEHRYFKANDTLGF (SEQ ID NO:110). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain tissues, such as cerebellum and fetal dura mater tissues, and in fetal tissues or early stage lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and/or psychological disorders, or lung diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:62 as residues: Val-89 to Leu-95, Pro-175 to Tyr-181.

The tissue distribution in fetal lung and brain tissues such as cerebellum and fetal dura mater, and the homology to a murine G-protein coupled receptor, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or intervention of neurological, psychological and respiratory diseases.

The G-protein coupled receptor can be used as a reagent for ligand screening, antagonist and agonist identification and development, or for the blocking of receptor mediated viral infection. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed
5 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the
10 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 914 of SEQ ID NO:13, b is an integer of 15 to 928, where both a and b correspond to the positions of nucleotide residues shown in
15 SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

20 The translation product of this gene shares some sequence homology with various chains of the T-cell receptor, which are important in signalling between different cells of the immune system. The gene encoding the disclosed cDNA is thought to reside on the X chromosome. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for the X chromosome.

25 This gene is expressed primarily in placental tissue, and to a lesser extent in activated monocytes and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
30 not limited to, immune disorders and reproductive disorders, particularly pregnancy-associated disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and female reproductive system, expression of this
35 gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
5 NO:63 as residues: Val-29 to Val-37, Asp-71 to His-76, Gln-78 to Gly-84, Met-105 to His-110, Trp-117 to Gly-122, Gln-136 to Lys-141, Leu-143 to Ala-149, Thr-162 to Asp-174, Ser-181 to Lys-186, Arg-214 to Glu-220, Glu-232 to Glu-238, Cys-249 to Asp-265.

The tissue distribution in dendritic cells, activated monocytes and placental
10 tissue (a tissue rich in hematopoietic cells), and its homology to the T-cell receptor, indicates that polynucleotides and polypeptides corresponding to this gene are useful in the treatment, prophylaxis and/or diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. Its expression predominantly in hematopoietic cells also
15 indicates that the gene could be important for the treatment and/or detection of hematopoietic disorders such as graft versus host reaction, graft versus host disease, transplant rejection, myelogenous leukemia, bone marrow fibrosis, and myeloproliferative disease.

The protein could also be used to enhance or protect the proliferation,
20 differentiation, and functional activation of hematopoietic progenitor cells such as bone marrow cells, which could be useful for cancer patients undergoing chemotherapy or patients undergoing bone marrow transplantation. The protein may also be useful as a means to increase the proliferation of peripheral blood leukocytes, which could be useful in the combat of a range of hematopoietic disorders including
25 immunodeficiency diseases, leukemia, and septicemia.

In addition, expression in placenta indicates the gene or the protein encoded by
this gene could be useful in the treatment, prophylaxis and/or diagnosis of placentitis, placenta previa, pregnancy disease, and miscarriage. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and
30 maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In
35 such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the

proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1576 of SEQ ID NO:14, b is an integer of 15 to 1590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

- 20 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GTSGTSGTRWNVHF (SEQ ID NO:111). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in infant brain tissue.

- 25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, neurodegenerative and behavioral diseases of the brain such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathies (TSE), Creutzfeldt-Jakob disease (CJD), specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive
- 30 behavior and sleep disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous
- 35 and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of developmental, degenerative and behavioral diseases and conditions of the brain such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), aphasia, depression, specific brain tumors, mania, dementia, paranoia, addictive behavior and sleep disorders. Furthermore, this gene product may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

The expression within infant tissue suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:15, b is an integer of 15 to

815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 6

This gene is expressed primarily in hepatocellular tumor tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatocellular tumors, hepatoblastoma, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, bile, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in hepatocellular tumor tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of liver cancers and conditions such as hepatocellular tumors, hepatoblastoma, jaundice, hepatitis, liver metabolic diseases, and other disorders that are attributable to the differentiation of hepatocyte progenitor cells. Furthermore, the tissue distribution indicates that the translation product of this gene is useful for the diagnosis and/or treatment of cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 976 of SEQ ID NO:16, b is an integer of 15 to 990, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 7

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DGAGAFRAPIREPGVPASPQPPEPGQLRRRQGHRRGGVG
 10 SPRTPAGGSRGRRLPATKRGTSGRRARGSSGRINASQT (SEQ ID NO:112), QH
 GLQILLQRDGVPGGDAGEPHGQXRGLHAQQLHRPVGSVDLWIFRVDAAGSGP
 XVXXGNELRHLQGLPGTVGHPRTMDETGPPAVGEPRSGPSAGSAGPTAAASP
 RPAATSPTGRAHIAGRCSQPTADDXPEFVCLKTLLLCLRMGEMRSEAPGAAXE
 KNNFYRDARDSRSGSGXGTGGNAACAQSPLPRTSKIRSKLRGRGWGCRGGDS
 15 EPPVRKQ (SEQ ID NO:113), QHGLQILLQRDGVPGGDAGEPHGQXRGLHAQQ
 LHRPVGSVDLWIFRVDA (SEQ ID NO:114), AGSGPXVXXGNELRHLQGLPGTV
 GHPRTMDETGPPAVGEPRSGPSAGS (SEQ ID NO:115), AGPTAAASPRPAATS
 PTGRAHIAGRCSQPTADDXPEFVCLKTLLLCLR (SEQ ID NO:116), MGEMRS
 EAPGAAXEKNNFYRDARDSRSGSGXGTGGNAACAQSPLPRTSK (SEQ ID
 20 NO:117), and/or IRSKLRGRGWGCRGGDSEPPVRKQ (SEQ ID NO:118).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in osteoblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as
 25 reagents for differential identification of the tissue(s) or cell type(s) present in a
 biological sample and for diagnosis of diseases and conditions which include, but are
 not limited to, skeletal disorders and diseases, particularly osteoporosis, osteosarcoma,
 osteonecrosis, arthritis, tendonitis, chondromalacia and inflammation. Similarly,
 polypeptides and antibodies directed to these polypeptides are useful in providing
 immunological probes for differential identification of the tissue(s) or cell type(s). For a
 30 number of disorders of the above tissues or cells, particularly of bone, expression of
 this gene at significantly higher or lower levels may be routinely detected in certain
 tissues or cell types (e.g., skeletal, osteoblasts, and cancerous and wounded tissues) or
 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or
 another tissue or cell sample taken from an individual having such a disorder, relative to
 35 the standard gene expression level, i.e., the expression level in healthy tissue or bodily
 fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:66 as residues: Pro-33 to Phe-43, Pro-48 to Lys-54, His-61 to Val-66.

5 The tissue distribution in osteoblasts indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of osteoporosis, fractures, osteosarcoma, ossification, osteonecrosis, trauma, arthritis, tendonitis, chondromalacia and inflammation. Furthermore, elevated levels of expression of this gene product in osteoblasts indicates that it may play a role in the survival, proliferation, and/or growth of osteoblasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1174 of SEQ ID NO:17, b is an integer of 15 to 1188, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 8

This gene is expressed primarily in brain and infant brain tissues, such as in the frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, degenerative and behavioral diseases of the brain such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathies (TSE), Creutzfeldt-Jakob disease (CJD), specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a
5 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in infant and adult brain tissues such as the frontal cortex indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of developmental, degenerative and behavioral diseases
10 and conditions of the brain such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), aphasia, depression, specific brain tumors, mania, dementia, paranoia, addictive behavior and sleep disorders. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it
15 may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's.

Moreover, the expression within infant tissue suggests this protein may play a
20 role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell
25 death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate
30 apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available
35 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1591 of SEQ ID NO:18, b is an integer of 15 to 1605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

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The translation product of this gene shares sequence homology with a C. elegans protein which may be involved in development (See GenBank Accession No.: AF038611). In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GTSPEAYVGGGPECP (SEQ ID NO:119).

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Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

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This gene is expressed primarily in adipocytes, early development stage tissues such as 8-week old embryonic tissues, immune tissues such as fetal liver/spleen, and cancerous tissues such as testes tumors, and to a lesser extent in some other tissues, such as prostate and testes.

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Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders, and particularly obesity, diabetes, growth disorders, and immune diseases or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adipocytes, early development stage tissues, immune tissues, and cancer tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., metabolic, developmental, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

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Preferred epitopes include those comprising a sequence shown in SEQ ID NO:68 as residues: Gly-19 to Ser-27, Gln-39 to Gly-45, Gln-48 to Ala-55, Ala-75 to Thr-80, Thr-198 to Gly-211.

- 5 The tissue distribution in developmental, immune, metabolic, and cancerous tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of obesity, diabetes, growth disorders, and immune diseases. The tissue distribution in testes, and tumor tissue thereof, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g.
- 10 endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene
- 15 expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.
- 20 Moreover, expression within 8-week old embryonic tissues and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation.
- 25 Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Additionally, expression of this gene product in fetal liver/spleen tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine
- 30 production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

- Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used
- 35 as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility

in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2075 of SEQ ID NO:19, b is an integer of 15 to 2089, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 10

- 20 This gene is expressed primarily in retinal tissue, and to a lesser extent in the amygdala of the brain.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, eye defects, neurological and behavioural disorders and diseases.
- 25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ocular and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., retinal, brain, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, vitreous
- 30 and aqueous humors, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 35 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:69 as residues: Ser-39 to Ser-46, Gly-60 to Gln-71.

The tissue distribution predominantly in retinal tissue indicates a role for this gene product in the treatment, prophylaxis and/or diagnosis of eye disorders including blindness, color blindness, short-sightedness, long-sightedness, retinitis pigmentosa, retinitis proliferans, retinoblastoma, retinochoroiditis, retinopathy and retinoschisis.

5 Expression in amygdala tissue in the brain indicates a role in the detection, treatment and/or prophylaxis of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Furthermore, the amygdala processes sensory information and relays this to other areas of the brain, including the endocrine and autonomic domains of the hypothalamus and the brain stem. Therefore, the translation product of this gene is likely to be involved in the processing of sensory information, for example, from the eyes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

20 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1267 of SEQ ID NO:20, b is an integer of 15 to 1281, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SCIHTGDMIXPVLSCFTRF (SEQ ID NO:120).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

When tested against U937 myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other immune cells, through the JAK-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the JAK-STAT pathway. The JAK-STAT pathway is a large, signal transduction pathway involved in the

differentiation and proliferation of cells. Therefore, activation of the JAK-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

This gene is expressed primarily in frontal cortex brain tissue from a schizophrenia patient and teratocarcinoma tissue, and to a lesser extent in placenta, osteoblast and embryonic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental or vascular disorders or defects. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system and embryonic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., nervous, embryonic, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:70 as residues: Thr-21 to Leu-26.

The tissue distribution in early development tissues (i.e., placental, embryonic) indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or intervention of developmental disorders, including the defects in nervous system and bone morphogenesis. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in

angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1747 of SEQ ID NO:21, b is an integer of 15 to 1761, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

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The translation product of this gene shares sequence homology with smaller hepatocellular oncoprotein (hhcm) gene product, which is thought to be important in the tumorigenesis of hepatocellular carcinoma. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GRHLVASQKRVLRD RRVQTGIWSDQLYSQRPWAPVTWPDHWGVCVCVYVC (SEQ ID NO:121). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in pancreas islet cell tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine or hepatic disorders, particularly pancreas islet cell tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pancreas, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pancreas, hepatic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, bile,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:71 as residues: Gly-26 to Lys-33, Lys-47 to His-52.

The tissue distribution in pancreas islet cell tumors, and the homology to the smaller hepatocellular oncoprotein (hhcm) gene product, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or
10 intervention of pancreas islet cell tumors and hepatocellular carcinomas, as well as preneoplastic or pathological conditions of the liver. Furthermore, the translation product of this gene is useful for the detection and/or treatment of cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets
15 for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the
20 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1175 of SEQ ID NO:22, b is an integer of 15 to 1189, where both a and b correspond to the positions of nucleotide residues shown
25 in SEQ ID NO:22, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

30 The translation product of this gene shares sequence homology with actinin, which is thought to be important in actin gelation. Recently another group has published a human gene which shares homology with this gene, calling it smoothelin (See Genbank Accession No.: gnllPID1284289). The gene encoding the disclosed cDNA is thought to reside on chromosome 22. Accordingly, polynucleotides related to this
35 invention are useful as a marker in linkage analysis for chromosome 22. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: AFPHSIPCQVMAVPSPQLLLRPXLPVSFMFLTSHPPPRLVCP (SEQ ID

NO:122) LPTLHSLSSYGCLTPAAPREALXTCVIHVS NKPPSTPSCVPHAPVHL
CCVGVGGPFAHAWGIPCPDQRDKERERRLQEARGRPGEGRGNTATETTTTRHS
QRAADGSAVSTVTKTERLVHSNDGTRTARTTTVESSFVRRSENGSGSTM MQTK
TFSSSSSSKKMGSIFDREDQASPRAGSLAALEKRQAEKKKELMKAQSLPKTSA
5 SQARKAMIEKLEKEGAAGSPGGPRAAVQRSTSFGV PNANSIKQMLLDWCRAK
TRGYEHVDIQNFSSSWSDGMAFCALVHNFFPEAFDYQLSPQNR RQNFEVAFS
SAETHADCPQLLDTEDMVRLREPDWKC VYTYIQEFYRCLVQKGLVKT KKS
(SEQ ID NO:123), LPTLHSLSSYGCLTPAAPREALXTCVIHVS NKPPSTPSCVP
HAPV (SEQ ID NO:124), HLCCVGVGGPFAHAWGIPCPDQRDKERERRLQE
10 ARGRPGEGRGNTA (SEQ ID NO:125), TETTTTRHSQRAADGSAVSTVTKTERL
VHSNDGTRTARTTTVESSFV (SEQ ID NO:126), RRENGSGSGSTM MQTKTFSSS
SSSKKMGSIFDREDQASPRAGSLAAL (SEQ ID NO:127), EKRQAEKKKELMKA
QSLPKTSASQARKAMIEKLEKEGAAGSPGGPRA (SEQ ID NO:128), AVQRSTS
FGV PNANSIKQMLLDWCRAKTRGYEHVDIQNFSSSWSDGM (SEQ ID NO:129),
15 AFCALVHNFFPEAFDYQLSPQNR RQNFEVAFSSAETHADCPQLLDTED (SEQ
ID NO:130), and/or MVRLREPDWKC VYTYIQEFYRCLVQKGLVKT KKS (SEQ ID
NO:131). Polynucleotides encoding these polypeptides are also encompassed by the
invention.

20 This gene is expressed primarily in kidney cortex, skeletal muscle, prostate and
to a lesser extent in many other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, skeletal muscle diseases or kidney diseases. Similarly, polypeptides and
25 antibodies directed to these polypeptides are useful in providing immunological probes
for differential identification of the tissue(s) or cell type(s). For a number of disorders
of the above tissues or cells, particularly of the skeletal muscle or kidney, expression of
this gene at significantly higher or lower levels may be routinely detected in certain
tissues or cell types (e.g., musculo-skeletal, kidney, and cancerous and wounded
30 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal
fluid) or another tissue or cell sample taken from an individual having such a disorder,
relative to the standard gene expression level, i.e., the expression level in healthy tissue
or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
35 NO:72 as residues: Ala-23 to Arg-36, His-38 to Ala-46, Pro-50 to Gly-56, Arg-85 to
Val-94.

The tissue distribution in skeletal muscle tissue, and the homology to actinin and smoothelin, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of skeletal muscle diseases, including muscular dystrophy, kidney diseases and prostate ailments. Additionally, the gene product can be used as a target for anti-tumor agent development. Furthermore, the tissue distribution in skeletal muscle tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1478 of SEQ ID NO:23, b is an integer of 15 to 1492, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

25

The gene encoding the disclosed cDNA is thought to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in hematopoietic tissues and cell types such as T cells, bone marrow, spleen, and lymphocytic leukemia, and to a lesser extent in testes and other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, immune, and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a

number of disorders of the above tissues or cells, particularly of the hematopoietic and immune tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:73 as residues: Tyr-22 to His-27, Ile-54 to Gln-60.

The tissue distribution in a wide variety of immune tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic, immune, and inflammatory disorders. Furthermore, the tissue distribution in a wide variety of immune tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells, bone marrow, and spleen tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1594 of SEQ ID NO:24, b is an integer of 15 to 1608, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

The translation product of this gene shares sequence homology with a putative transmembrane protein from *Helicobacter pylori* (GeneSeq Accession No.: W20765). In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: KMEWLADPTAWLGLLTLIVLXLVLGIDNLVFIXIXAXKLPPEQR DRARLIGLSLALLMRLGLLASISWLVTLTQPLFEVFDKSFSGRDLIMLFGGVFLL FKATMELHERLEGHVAQRTGNVAYAMFWPIVAQIVVLDAVFSLDAVITAVGMV DELAVMMIAXIISIGLMIVASKPLTRFVNAHPTVIMLCLGFLMMIGFALTAEGLG FHIPKGYLYAAIGFSILIELFNQIARSRRKKSQAQGTLP RRERTAHAVMRLLGGR NLAVEEVGEEVADLLDNPDANGGPLFDRRERVMISGVLQLAERPRTLMTPRAK VDSIDLSDDPXTIRLKLXIRLTRACP (SEQ ID NO:132), KMEWLADPTAWLGLL TLIVLXLVLGIDNLVFIXIXAXKLPPEQRDRAR (SEQ ID NO:133), LIGLSLALL MRLGLLASISWLVTLTQPLFEVFDKSFSGRDLIMLFGGVF (SEQ ID NO:134), LLFKATMELHERLEGHVAQRTGNVAYAMFWPIVAQIVVLDAVFSLDA (SEQ ID NO:135), VITAVGMVDELAVMMIAXIISIGLMIVASKPLTRFVNAHPTVIMLCLGF (SEQ ID NO:136), LMMIGFALTAEGLGFHIPKGYLYAAIGFSILIELFNQIARSRR KKSQAQGT (SEQ ID NO:137), LRRERTAHAVMRLLGGRNLAVEEVGEEVADLL DNPDANGGPLFDRRE (SEQ ID NO:138), and/or RVMISGVLQLAERPRTLMTPR AKVDSIDLSDDPXTIRLKLXIRLTRACP (SEQ ID NO:139). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in CD34 positive cord blood cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoiesis or developmental disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of CD34 positive cells, expression of this gene at significantly higher or lower levels may be routinely detected

in certain tissues or cell types (e.g., immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:74 as residues: Asp-34 to Pro-46.

The tissue distribution in CD34 positive cord blood cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoiesis disorders. Expression of this gene product in CD34 positive cord blood cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1950 of SEQ ID NO:25, b is an integer of 15 to 1964, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

5 The translation product of this gene shares sequence homology with atrophin-1, which is thought to be important in dentatorubral and pallidoluylsian atrophy (DRPLA), a progressive neurological disorder characterized by neuronal degeneration.

This gene is expressed primarily in fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural or developmental disorders and diseases, particularly neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:75 as residues: Asn-20 to Gly-27, Ser-49 to Trp-54, Leu-95 to Thr-101, Ala-140 to Pro-148.

25 The tissue distribution in fetal brain tissue, and the homology to atrophin-1, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of neurodegenerative diseases, including dentatorubral and pallidoluylsian atrophy (DRPLA), and Huntington's disease. Additionally, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein

may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 919 of SEQ ID NO:26, b is an integer of 15 to 933, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 17

The translation product of this gene shares sequence homology with a C. elegans protein F25H2.12 which may be involved in development (See GenBank Accession No.: gnllPIDle264283). In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LLTSPVSWHSTVPSW (SEQ ID NO:140). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in tumors, such as lung tumors, in immune tissues and cell types such as fetal liver/spleen tissues, and in brain tissue such as infant brain tissue, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders and diseases, tumorigenesis, immune and inflammatory disorders, and neural diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tumor, immune tissues and cell types, and brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken

from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID

- 5 NO:76 as residues: Thr-3 to Ser-8, Pro-30 to Pro-35, Asn-41 to Arg-47, Val-56 to His-62, Val-71 to Asp-76.

- 10 The tissue distribution in immune, neural, and cancerous tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of tumors, immune and inflammatory disorders, and neural diseases. The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning
- 15 disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

- 20 Alternatively, the expression of this gene product in fetal liver/spleen tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of
- 25 lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In
- 30 addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, the tissue distribution in cancerous tissues, such as cancerous lung tissue, indicates that the translation product of this gene is useful for the diagnosis and/or treatment of lung cancers, as well as cancers of other
- 35 tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1223 of SEQ ID NO:27, b is an integer of 15 to 1237, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ŠALSISNHQGFF (SEQ ID NO:141). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in activated T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:77 as residues: His-16 to Asn-24, Trp-36 to Ala-43, His-59 to Leu-66, Glu-82 to Gly-90, Ser-113 to Trp-123, Pro-145 to Thr-154, Ala-164 to Pro-176.

The tissue distribution of this gene primarily in activated T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prophylaxis and/or diagnosis of immune and autoimmune diseases, such as

lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, AIDS and that it may also play a role in the treatment, prophylaxis and detection of thymus disorders such as Graves Disease, lymphocytic thyroiditis, hyperthyroidism and hypothyroidism. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis.

In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:28, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates

fibroblast cells, and to a lesser extent other musculo-skeletal cells, through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

5 This gene is expressed primarily in testes tissue.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive and endocrine disorders, as well as testicular cancer.

10 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes, reproductive, and
15 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:78 as residues: Gly-33 to Ser-44.

 The tissue distribution in testes tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of male reproductive and endocrine disorders. It may also prove to be valuable in the
25 diagnosis and treatment of testicular cancer, as well as cancers of other tissues where expression has been observed. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in
30 the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the
35 body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target

indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1053 of SEQ ID NO:29, b is an integer of 15 to 1067, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 20

This gene is expressed primarily in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prophylaxis and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. The gene or gene product may also play a role in the treatment, prophylaxis and/or detection of thymus disorders such as Graves Disease, lymphocytic thyroiditis, hyperthyroidism and hypothyroidism. Expression of this gene product in T cells also

strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:30, b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tonsillitis and immune disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:80 as residues: Pro-35 to Ser-40.

The tissue distribution of this gene in tonsils, a lymphoid tissue, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prophylaxis and/or diagnosis of immune and autoimmune diseases, in addition to tonsillitis and tonsilopharyngitis. Expression of this gene product indicates a

role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1416 of SEQ ID NO:31, b is an integer of 15 to 1430, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene is expressed primarily in the corpus striatum (of patient suffering from depression), as well as in bone marrow tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders and diseases, particularly behavioral disorders (e.g. depression) and hematopoietic disorders (e.g. anemias and immune deficiencies). Similarly, polypeptides and antibodies directed to these polypeptides are useful in

providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, immune, and cancerous
5 and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
10 NO:81 as residues: His-29 to Asn-34.

The tissue distribution in corpus striatum tissue of the brain and in bone marrow tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of patients suffering from depression, but also perhaps other brain disorders and conditions such as schizophrenia, Alzheimer's
15 disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), aphasia, specific brain tumors, mania, dementia, paranoia, addictive behavior and sleep disorders. In addition, the expression in bone marrow tissue indicates a role for the protein product of this gene in immune deficiencies, anemias and other hematopoietic conditions. Furthermore,
20 the tissue distribution in bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia.

The uses include bone marrow cell ex vivo culture, bone marrow
25 transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation
30 and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ
35 ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:32, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells, or more generally, integumentary cells, in addition to other cells and cell types, through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The gene encoding the disclosed cDNA is thought to reside on chromosome 20. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 20.

This gene is expressed primarily in placental tissue, endometrial cells and breast tissue, and to a lesser extent in a variety of other tissues and cell types.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental anomalies, fetal deficiencies, endometrial cancers and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, developmental, placental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in placental tissue, endometrial tissue, and breast tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of developmental abnormalities, fetal deficiencies,

reproductive disorders and ovarian or other endometrial cancers, as well as cancers of other tissues where expression has been observed. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within
5 the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.

Expression of this gene product in a vascular-rich tissue such as the placenta
10 also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of
15 hematopoietic cells, as well as other cells throughout the body.

Additionally, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions
20 involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available
25 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more
30 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1488 of SEQ ID NO:33, b is an integer of 15 to 1502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HKGSGRPPTKEAMEPMELMEEMLGLWVSADTP (SEQ ID NO:142). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fast growing tissues and cell types such as early developmental stage tissues (12-week old embryonic tissues), immune tissues such as T-cells and bone marrow, and tumor tissues such as skin tumors, and to a lesser extent in other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders, immune diseases, and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fast growing tissues and cell types such as early stage developmental tissues, immune tissues, and tumor tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:83 as residues: Asp-26 to Asn-31, Ser-37 to His-49, Ala-65 to Ser-73.

The tissue distribution in immune, developing, and cancerous tissues indicates that the protein product of this gene is useful for the diagnosis and/or treatment of developmental disorders, immune diseases, and tumors. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of immune system disorders. Expression of this gene product in T-cells and bone marrow indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may

also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in skin tumors indicates that the translation product of this gene is useful for the diagnosis and/or treatment of skin tumors, as well as tumors of other tissues where expression has been observed.

Moreover, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 713 of SEQ ID NO:34, b is an integer of 15 to 727, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

35

The translation product of this gene shares sequence homology with a number of glycoprotein proteases from parasites such as Leishmania and Trypanosomes. In

addition, a zinc protease domain has been identified as TVKHEVIHAL (SEQ ID NO:143). Preferred polypeptides of the invention comprise the following sequence (sequence A), or a fragment thereof which retains the biological activity of a polypeptide comprising the entire sequence. Protease activities are the preferred biological activity. Assays for determining protease activity are known in the art. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: EXLLPEKKNLVKNKLLXXAISYLEKTFQVRRPAGTILLSRQCATNQ YLRKENDPHRYCTGECAAHTKCGPVIVPEEHLQQCRVYRGGKWPHGAVGVPDQEGISDADFVLYVGALATERCSHENIISYAAAYCQQEANMDRPIAGYANLCPNM ISTQPQEFVGMSTVKHEVIHALGFSAGLFAFYHDKDGNPLTSRFADGLPPFNY SLGLYQWSDKVVRKVXRLWDVRDNKIVRHTVYLLVTPRVVEEARKHFDCPVLEGMELNQGGVGTELNHWEKRLLENEAMTGSHTQNRVLSRITLALMEDTGWY KANYSMAEKLDWGRGMGCDVVRKSKCFWIDQQRQKRQMLSPYCDTLRSNPL QLTQRQDQRAVAVCNLQKFKPLPQEYQYFDELSGIPAEDLPYYGGSVEIADYX PFSQEFSWHLSGEYQRSSDCRILENQPEIFKNYGAEKYGPHSVCLIQKSAFVME KCERKLSYPDWGS GCYQVSCSPQGLKVWVQDTSYLCSRAGQVLPVSIQMNG WIHDGNLLCPSCWDFCELCPPETDPPATNLTRALPLDLCSCSS (SEQ ID NO:144), EXLLPEKKNLVKNKLLXXAISYLEKTFQVRRPAGTILLSRQCATNQY (SEQ ID NO:145), LRKENDPHRYCTGECAAHTKCGPVIVPEEHLQQCRVYRGG KWPHG (SEQ ID NO:146), AVGVDPQEGISDADFVLYVGALATERCSHENIISY AAYCQQEANM (SEQ ID NO:147), DRPIAGYANLCPNMISTQPQEFVGMSTVKH EVIHALGFSAGLFAF (SEQ ID NO:148), YHDKDGNPLTSRFADGLPPFNYSLGL YQWSDKVVRKVXRLWDVRD (SEQ ID NO:149), NKIVRHTVYLLVTPRVVEEAR KHFDKCPVLEGMELNQGGVGTELNH (SEQ ID NO:150), WEKRLLENEAMTGS HTQNRVLSRITLALMEDTGWYKANYSMAEKL (SEQ ID NO:151), DWGRGMG CDFVRKSKCFWIDQQRQKRQMLSPYCDTLRSNPLQLTC (SEQ ID NO:152), RQDQRAVAVCNLQKFKPLPQEYQYFDELSGIPAEDLPYYGGSVEIA (SEQ ID NO:153), DYXPFSQEFSWHLSGEYQRSSDCRILENQPEIFKNYGAEKYGPHSV CL (SEQ ID NO:154), IQKSAFVMEK CERKLSYPDWGS GCYQVSCSPQGLKVW VQDTSYLCS (SEQ ID NO:155), and/or RAGQVLPVSIQMNGWIHDGNLLCPSCW DFCELCPPETDPPATNLTRALPLDLCSCSS (SEQ ID NO:156). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes tissue and T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders and/or male infertility. Similarly, polypeptides and

antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and male reproductive system, expression of this gene at significantly higher or lower levels may be routinely
5 detected in certain tissues or cell types (e.g., immune, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the
10 disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:84 as residues: Met-1 to Gly-6, Arg-11 to Gly-21.

The tissue distribution in testes tissue and T-cells, and the homology to a cell surface marker, indicates that polynucleotides and polypeptides corresponding to this
15 gene are useful for the treatment, prophylaxis and/or detection of male infertility, in addition to immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. The translation product of this gene may also play a role in the treatment, prophylaxis and/or detection of thymus disorders such as Graves Disease, lymphocytic thyroiditis,
20 hyperthyroidism and hypothyroidism. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the
25 treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS,
30 leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells strongly indicates a role for this protein in immune function and immune
35 surveillance.

Furthermore, the tissue distribution in testes tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis

of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1977 of SEQ ID NO:35, b is an integer of 15 to 1991, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 26

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: IKEKLHVHG (SEQ ID NO:157). Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 This gene is expressed primarily in brain tissue, such as the amygdala.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and behavioural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system expression of this gene

at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:85 as residues: Arg-30 to Tyr-39.

The tissue distribution exclusively in brain tissues such as the amygdala indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntintons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. The amygdala processes sensory information and relays this to other areas of the brain including the endocrine and autonomic domains of the hypothalamus and the brain stem. Therefore, The translation product of this gene may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2307 of SEQ ID NO:36, b is an integer of 15 to 2321, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GFGVYILYA (SEQ ID NO:158). Polynucleotides encoding these polypeptides are also encompassed by the invention. When tested against U937

Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other immune system cells, through the JAK-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the JAK-STAT pathway. The JAK-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the JAK-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

10 This gene is expressed primarily in early development stage tissues and anergic T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, growth and developmental disorders and immune and inflammatory diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the early development stage tissues and anergic T cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in embryonic and immune tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of growth and developmental disorders and immune and inflammatory diseases. The tissue distribution in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

35 This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against

the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1544 of SEQ ID NO:37, b is an integer of 15 to 1558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: KPSGTVYTLFSLNSGTL (SEQ ID NO:159). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in some activated peripheral blood cells and disease tissues such as melanoma, multiple sclerosis, and osteosarcoma, and to a lesser extent in some other tissues such as gall bladder tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and inflammatory disorders and various diseases such as melanoma, multiple sclerosis, and osteosarcoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the peripheral blood cells and tissues affected by disease such as melanoma, multiple sclerosis, and osteosarcoma, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., peripheral blood cells, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, bile, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution peripheral blood cells, melanoma tissue, multiple sclerosis tissue, and osteosarcoma tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of immune and inflammatory disorders, and multiple sclerosis. Furthermore, the tissue distribution indicates that the translation product of this gene is useful for the treatment and/or diagnosis of various cancers, such as melanomas and osteosarcomas, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1687 of SEQ ID NO:38, b is an integer of 15 to 1701, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

This gene is expressed primarily in adipose tissue and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as
5 reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, metabolic and immune disorders or diseases, particularly obesity.
Similarly, polypeptides and antibodies directed to these polypeptides are useful in
providing immunological probes for differential identification of the tissue(s) or cell
10 type(s). For a number of disorders of the above tissues or cells, particularly of the
immune, metabolic and digestive systems, expression of this gene at significantly
higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,
immune, metabolic, digestive, and cancerous and wounded tissues) or bodily fluids
(e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or
15 cell sample taken from an individual having such a disorder, relative to the standard
gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an
individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
NO:88 as residues: Ile-40 to Glu-45, Cys-63 to Val-69, Glu-83 to Asn-94, Pro-107 to
20 Cys-115, Phe-137 to Ser-143, Ser-159 to Thr-167, Glu-200 to Tyr-210.

The tissue distribution in primarily adipose tissue indicates that polynucleotides
and polypeptides corresponding to this gene are useful for the treatment, diagnosis
and/or prophylaxis of obesity related disorders. In addition, expression in dendritic
cells indicates a potential role in the treatment, diagnosis and/or prophylaxis of immune
25 and autoimmune disorders such as lupus, transplant rejection, allergic reactions,
arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS.

The tissue distribution in adipose tissue indicates that polynucleotides and
polypeptides corresponding to this gene are useful for the treatment of obesity and other
metabolic and endocrine conditions or disorders. Furthermore, the protein product of
30 this gene may show utility in ameliorating conditions which occur secondary to aberrant
fatty-acid metabolism (e.g. aberrant myelin sheath development), either directly or
indirectly. Expression of this gene product in dendritic cells indicates a role in the
regulation of the proliferation; survival; differentiation; and/or activation of potentially
all hematopoietic cell lineages, including blood stem cells. This gene product may be
35 involved in the regulation of cytokine production, antigen presentation, or other
processes that may also suggest a usefulness in the treatment of cancer (e.g. by
boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1889 of SEQ ID NO:39, b is an integer of 15 to 1903, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 30

The translation product of this gene shares sequence homology with ATP-dependent RNA helicases, which are thought to be important in RNA binding and nucleic acid metabolism. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ADLTAVCSAWKPGAKPVGL (SEQ ID NO:160). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 22. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 22.

This gene is expressed primarily in ovary tumor, infant adrenal gland and white fat tissues, and to a lesser extent in many other tissues including bladder, endometrial stromal cells, Jurkat cells, pineal gland, and infant brain tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the ovary or adrenal gland. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:89 as residues: Gln-66 to Cys-71, Thr-76 to Gly-81, His-87 to Asp-92.

The tissue distribution in the ovary and adrenal gland tissues, and the homology to ATP-dependent RNA helicases, indicates that polynucleotides and polypeptides corresponding to this gene are useful as a hormone and/or endocrine with either systemic or reproductive functions, as growth factors for germ cell maintenance and in vitro culture, and as a tool for fertility control. Furthermore, the translation product of this gene is useful for the detection and/or treatment of sexual dysfunction or sex development disorders as well as ovarian tumors, such as serous adenocarcinoma, dysgerminoma, embryonal carcinoma, choriocarcinoma, and teratoma, for example. The tissue distribution of the gene product may also indicate its function as a hormone. Additionally, the homology to ATP-dependent RNA helicases indicates that the translation product of this gene may be utilized for the intervention of RNA viral infections. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1266 of SEQ ID NO:40, b is an integer of 15

to 1280, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene shares limited sequence homology with urokinase inhibitor, which is thought to be important in the inhibition of urokinase enzymatic activity.

10 This gene is expressed primarily in frontal cortex tissue of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative and cardiovascular disorders and diseases. Similarly,
15 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, cardiovascular, and cancerous and
20 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
25 NO:90 as residues: Pro-31 to Pro-37.

The tissue distribution in frontal cortex tissue of the brain, and the homology to urokinase inhibitor, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or intervention of neurodegenerative diseases, in preventing tumour metastasis, in ovulation and uterine ovum implantation, and as
30 anti-neoplastic agents. Furthermore, elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. The protein is
35 useful for the detection, treatment, and/or prevention of cardiovascular diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1904 of SEQ ID NO:41, b is an integer of 15 to 1918, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

When tested against sensory neuronal cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates sensory neuron cells, and to a lesser extent other neuronal cells, in addition to other cells or cell types, through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in frontal cortex tissue of the brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in frontal cortex tissue of the brain, in conjunction with the biological activity data, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of neural

disorders. Elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1254 of SEQ ID NO:42, b is an integer of 15 to 1268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

25 This gene is expressed primarily in synovial membrane and adipose tissues, as well as in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal disorders, synovioma, synovitis, obesity, and immune disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and metabolic systems, and the body's connective tissue, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., musculo-skeletal, immune, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
5 NO:92 as residues: Ser-24 to Cys-31, Gln-40 to Gly-51, Leu-71 to Met-76.

The tissue distribution of this gene primarily in synovial fluid, in adipose tissue, and in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, detection and/or prophylaxis of disease states associated with these cell types including synovioma, synovitis, obesity, immune and
10 autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. The tissue distribution in adipose tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of obesity and other metabolic and endocrine conditions or disorders. Furthermore, the protein product of this gene may show utility
15 in ameliorating conditions which occur secondary to aberrant fatty-acid metabolism (e.g. aberrant myelin sheath development), either directly or indirectly.

In addition, the expression of this gene product in synovium indicates a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or
20 treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal
25 chondrodysplasia type Schmid).

Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may
30 also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency
35 diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis.

In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein is useful in modulating the immune response, particularly to proliferating or aberrant cells or cell-types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1187 of SEQ ID NO:43, b is an integer of 15 to 1201, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene is expressed primarily in brain and pancreas tumor tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural diseases and tumors, particularly of the pancreas. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain tissue and pancreas tumor, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, metabolic, pancreas, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, bile, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:93 as residues: Thr-50 to Phe-55.

5 The tissue distribution in brain tissue and pancreatic tumor tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of neural diseases and tumors, particularly pancreatic tumors. The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, 10 dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Alternatively, the 15 tissue distribution in pancreatic tumor tissue indicates that the translation product of this gene is useful for the detection and/or treatment of pancreatic tumors, as well as tumors of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. 25 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 805 of SEQ ID NO:44, b is an integer of 15 to 819, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

35 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: TTWATSSVVARXTHHLFPPHSGISVNIQDLAPSCAGFLFG VANTAGALAGVVGVCCLGGYL (SEQ ID NO:162). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal liver/spleen tissue, and to a lesser extent in a variety of other tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders and diseases, including leukemias, lymphomas, arthritis and asthma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:94 as residues: Met-1 to Ser-6, Ser-38 to Leu-43.

The tissue distribution in fetal liver/spleen tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-suppressive conditions (e.g. transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer. Furthermore, expression of this gene product in fetal liver/spleen tissues indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the

differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1552 of SEQ ID NO:45, b is an integer of 15 to 1566, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene is expressed primarily in infant brain tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural and/or developmental disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in infant brain tissue indicates that the product of this gene is useful for the diagnosis and/or treatment of central nervous system and neurodegenerative disorders. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease,

Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product
5 may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Moreover, the expression within infant tissue suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues
10 rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the
15 polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies
20 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available
25 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more
30 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2080 of SEQ ID NO:46, b is an integer of 15 to 2094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

This gene is expressed primarily in apoptotic T-cells and T-cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as
5 reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are
not limited to, immune or hematopoietic disorders and diseases, particularly those
relating to T-cell disorders, such as immunodeficiencies. Similarly, polypeptides and
antibodies directed to these polypeptides are useful in providing immunological probes
10 for differential identification of the tissue(s) or cell type(s). For a number of disorders
of the above tissues or cells, particularly of the immune system, expression of this gene
at significantly higher or lower levels may be routinely detected in certain tissues or cell
types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily
fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another
15 tissue or cell sample taken from an individual having such a disorder, relative to the
standard gene expression level, i.e., the expression level in healthy tissue or bodily
fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID
NO:96 as residues: Cys-32 to Asn-37.

20 The tissue distribution in T-cells and T-cell lymphoma indicates that
polynucleotides and polypeptides corresponding to this gene are useful for the
diagnosis and/or treatment of immune system disorders. Expression of this gene
product in T-cells indicates a role in the regulation of the proliferation; survival;
differentiation; and/or activation of potentially all hematopoietic cell lineages, including
25 blood stem cells. This gene product may be involved in the regulation of cytokine
production, antigen presentation, or other processes that may also suggest a usefulness
in the treatment of cancer (e.g. by boosting immune responses). Since the gene is
expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies
directed against the protein may show utility as a tumor marker and/or immunotherapy
30 targets for the above listed tissues.

Therefore it may be also used as an agent for immunological disorders including
arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid
arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene
product may have commercial utility in the expansion of stem cells and committed
35 progenitors of various blood lineages, and in the differentiation and/or proliferation of
various cell types. Expression of this gene product in T cells also strongly indicates a
role for this protein in immune function and immune surveillance. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 942 of SEQ ID NO:47, b is an integer of 15 to 956, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

15 FEATURES OF PROTEIN ENCODED BY GENE NO: 38

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DSPLTVLPEDGYGSDSHLSSQVVRGPT (SEQ ID NO:163). Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 This gene is expressed primarily in activated T-cells and human testes tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders relating to the immune system, and T-cells in particular, as well as male reproductive diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:97 as residues: Arg-23 to Ser-34.

The tissue distribution in testes tumor tissue and T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of immune and male reproductive disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1701 of SEQ ID NO:48, b is an integer of 15 to 1715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

10 The translation product of this gene shares sequence homology with the human PEX gene (See Genbank Accession No.: Y10196). In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: VEAIFSE LVIVLNKMSHCVLSGT (SEQ ID NO:164). Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in amniotic cells, ovarian cancer, and fetal heart tissue.

 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive and developmental diseases or disorders and diseases of the circulatory system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, reproductive and circulatory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., central nervous system, reproductive, circulatory, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 The tissue distribution in fetal heart, ovarian cancer, and amniotic cells, and the homology to human PEX gene, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of diseases of the central nervous system, reproductive and circulatory systems. The tissue distribution in fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular

system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Furthermore, the tissue distribution in ovarian cancer tissue indicates that the translation product of this gene is useful for the diagnosis and/or treatment of ovarian cancer, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1447 of SEQ ID NO:49, b is an integer of 15 to 1461, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: KPTKMPLLWVWALIAAVSQPELWYRE (SEQ ID NO:165). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in ovarian tumor, tissue affected by multiple sclerosis, and bladder tissue from a female.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in female reproductive and urinary systems, and nervous system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive, urinary, and central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain

tissues or cell types (e.g., reproductive, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:99 as residues: Phe-25 to Ser-30.

The tissue distribution in ovarian tumor tissue, bladder and multiple sclerosis tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of reproductive, urinary, and central nervous systems disorders. The tissue distribution in ovarian cancer tissue indicates that the translation product of this gene is useful for the detection and/or treatment of ovarian cancer, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1224 of SEQ ID NO:50, b is an integer of 15 to 1238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in stromal cells, and was found in a cDNA library derived from fetal liver and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, disorders in connective tissue, and the immune and hematopoietic systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscular and skeletal system, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, musculo-skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:100 as residues: Pro-28 to Ser-37.

The tissue distribution in stromal cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of connective tissue and immune system disorders. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2567 of SEQ ID NO:51, b is an integer of 15

to 2581, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 42

This gene is expressed primarily in infant brain and ovarian cancer, and to a lesser extent in adrenal gland tumor tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in the nervous system and female reproductive system, as well as cancers. Similarly, polypeptides and antibodies directed to these polypeptides are
15 useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, endocrine, and female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, reproductive, endocrine, and cancerous and wounded
20 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:101 as residues: Leu-24 to Ser-29.

25 The tissue distribution in infant brain tissue and cancerous tissues of ovarian and adrenal gland nature indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of central nervous system and female reproductive system disorders. The tissue distribution in cancerous tissues of the ovaries and adrenal glands indicates that the translation product of this gene is useful for
30 the detection and/or treatment of cancers of the endocrine (adrenal glands) and female reproductive (ovaries) systems, as well as cancers of other tissues and systems where expression has been observed. Alternatively, the tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders
35 such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors,

including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 977 of SEQ ID NO:52, b is an integer of 15 to 991, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

This gene is expressed primarily in fetal liver/spleen tissue, and to a lesser extent in placental tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoiesis disorders, and proper placental maintenance. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developing systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, placental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:102 as residues: Cys-44 to Gly-49.

The tissue distribution in fetal liver/spleen and placental tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of immune disorders. The tissue distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are
5 useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or
10 fetus.

Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature
15 and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders.

20 Expression of this gene product in fetal liver/spleen tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the
25 treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS,
30 leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy
35 targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more
- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2408 of SEQ ID NO:53, b is an integer of 15 to 2422, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 44

This gene is expressed primarily in neutrophils.

- Therefore, polynucleotides and polypeptides of the invention are useful as
- 15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neutropenia and neutrophilia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of
- 20 the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
- 25 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of immune system disorders. Expression of this gene product in neutrophils indicates a
- 30 role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin,
- 35 the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma,

immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis.

In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 971 of SEQ ID NO:54, b is an integer of 15 to 985, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

20

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

This gene is expressed primarily in the prostate tissue and in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and prostate disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, male reproductive and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., prostate, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:104 as residues: Tyr-34 to Val-41.

The tissue distribution of this gene in T-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, prophylaxis and/or diagnosis of immune and autoimmune diseases, such as lupus (SLE), transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. In addition may also play a role in the treatment, prophylaxis and detection of thymus disorders such as Grave's Disease, lymphocytic thyroiditis, hyperthyroidism and hypothyroidism. Expression in T-cells also indicates potential as growth factor which could be used to boost specific populations of immune cells including T-cells and B-cells. Expression in the prostate indicates a role in the treatment, prophylaxis and detection of prostate disorders including prostate cancer, prostatism, prostatitis, prostaticorrhea and prostatovesiculitis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1750 of SEQ ID NO:55, b is an integer of 15 to 1764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	S' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HDPOW86	209603 01/29/98	pCMVSPORT 3.0	11	1810	58	1810	192	192	60	1	18	19	307
2	HSYAG26	209603 01/29/98	pCMVSPORT 3.0	12	2353	31	1721	39	39	61	1	22	23	578
3	HLHCH40	209603 01/29/98	Uni-ZAP XR	13	928	1	928	43	43	62	1	13	14	184
3	HLHCH40	209603 01/29/98	Uni-ZAP XR	56	932	13	932	53	53	105	1	16	17	122
4	HSDEK49	209603 01/29/98	Uni-ZAP XR	14	1590	96	1590	126	126	63	1	21	22	305
5	HLMBO76	209603 01/29/98	Lambda ZAP II	15	815	1	795	43	43	64	1	43	44	107
6	HLQDR48	209603 01/29/98	Lambda ZAP II	16	990	1	990	3	3	65	1	21	22	190

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
7	HOBY12	209603 01/29/98	pCMVSPORT 2.0	17	1188	1	1188	232	232	66	1	25	26	199
8	HOSEK86	209603 01/29/98	Uni-ZAP XR	18	1605	1	1605	81	81	67	1	35	36	61
9	HABZ75	209603 01/29/98	pCMVSPORT 3.0	19	2089	10	2085	49	49	68	1	22	23	607
10	HAGCH75	209603 01/29/98	Uni-ZAP XR	20	1281	1	1281	80	80	69	1	17	18	89
11	HE8MH91	209603 01/29/98	Uni-ZAP XR	21	1761	1	1761	63	63	70	1	23	24	116
12	HISCJ55	209603 01/29/98	pSPORT1	22	1189	1	1189	151	151	71	1	21	22	139
13	HKISB57	209603 01/29/98	pBluescript	23	1492	1	1439	130	130	72	1	20	21	95
14	HTEBJ71	209603 01/29/98	Uni-ZAP XR	24	1608	1	1608	51	51	73	1	20	21	77

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
15	HCWKR01	209603 01/29/98	ZAP Express	25	1964	1	1964	65	65	74	1	28	29	54
16	HFCEW05	209603 01/29/98	Uni-ZAP XR	26	933	1	933	34	34	75	1	18	19	209
17	HCEPF19	209603 01/29/98	Uni-ZAP XR	27	1237	51	1224	292	292	76	1	25	26	104
18	HTACZ01	209603 01/29/98	Uni-ZAP XR	28	960	1	960	60	60	77	1	17	18	176
18	HTACZ01	209603 01/29/98	Uni-ZAP XR	57	957	1	957	53	53	106	1	17	18	55
19	HUDAM89	209603 01/29/98	ZAP Express	29	1067	1	1067	15	15	78	1	20	21	44
20	HSAXF60	209603 01/29/98	Uni-ZAP XR	30	1063	1	1063	198	198	79	1	21	22	70
21	HTOGR42	209603 01/29/98	Uni-ZAP XR	31	1430	1	1430	14	14	80	1	18	19	56

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
21	HTOGR42	209603 01/29/98	Uni-ZAP XR	58	1433	1	1433	13	13	107	1	18	19	60
22	HMVBN46	209603 01/29/98	pSport1	32	1382	1	1382	10	10	81	1	19	20	48
23	HUVEB53	209603 01/29/98	Uni-ZAP XR	33	1502	1	1502	14	14	82	1	20	21	45
24	HSVBU91	209603 01/29/98	Uni-ZAP XR	34	727	1	727	256	256	83	1	18	19	90
25	HTXFL30	209603 01/29/98	Uni-ZAP XR	35	1991	1	1991	30	30	84	1	39	40	102
26	HAGAM64	209603 01/29/98	Uni-ZAP XR	36	2321	1	2321	57	57	85	1	31	32	44
27	HE2PH36	209603 01/29/98	Uni-ZAP XR	37	1558	1	1558	28	28	86	1	21	22	66
28	HGBDY06	209603 01/29/98	Uni-ZAP XR	38	1701	48	1701	196	196	87	1	23	24	71

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
29	HWBAO62	209603 01/29/98	pCMVSPORT 3.0	39	1903	1	1903	52	52	88	1	30	31	212
29	HWBAO62	209603 01/29/98	pCMVSPORT 3.0	59	1940	1	1940	81	81	108	1	30	31	100
30	HBAFJ33	209603 01/29/98	pSport1	40	1280	1	1252	60	60	89	1	15	16	110
31	HFXDJ75	209603 01/29/98	Lambda ZAP II	41	1918	1	1914	44	44	90	1	26	27	41
32	HFPCY04	209603 01/29/98	Uni-ZAP XR	42	1268	1	1268	201	201	91	1	32	33	58
33	HSNBG78	209603 01/29/98	Uni-ZAP XR	43	1201	247	1188	291	291	92	1	21	22	76
34	HBQAB27	209603 01/29/98	Lambda ZAP II	44	819	1	819	119	119	93	1	21	22	68
35	HTOJY21	209603 01/29/98	Uni-ZAP XR	45	1566	205	1566	317	317	94	1	31	32	43

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT of Start Codon	S' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
36	HHTMM30	209603 01/29/98	ZAP Express	46	2094	1	2094	71	71	95	1	18	19	46
37	HLTAF58	209603 01/29/98	Uni-ZAP XR	47	956	1	956	103	103	96	1	30	31	47
38	HHEPU32	209603 01/29/98	pCMVSPORT 3.0	48	1715	1	1715	124	124	97	1	18	19	153
39	HHFDM48	209603 01/29/98	Uni-ZAP XR	49	1461	1	1461	139	139	98	1	34	35	45
40	HKABI84	209603 01/29/98	pCMVSPORT 2.0	50	1238	45	1238	274	274	99	1	16	17	47
41	HMVAX72	209603 01/29/98	pSPORT1	51	2581	1	2581	23	23	100	1	29	30	50
42	HODDN60	209603 01/29/98	Uni-ZAP XR	52	991	1	991	34	34	101	1	19	20	40
43	HPMEI44	209603 01/29/98	Uni-ZAP XR	53	2422	563	2422	578	578	102	1	39	40	49

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
44	HNGJP69	209603 01/29/98	Uni-ZAP XR	54	985	1	985	321	321	103	1	14	15	74
45	HPWBA10	209603 01/29/98	Uni-ZAP XR	55	1764	1	1764	16	16	104	1	18	19	42

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

- 5 The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.
- 10

Signal Sequences

- 15 Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra.*) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.
- 20

- 25 In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.
- 30

- 35 As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

10 Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4. Mismatch Penalty=1. Joining Penalty=30. Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See. Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid

substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a

larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Epitopes & Antibodies

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein

molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)

- 5 Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

- 10 In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

- 15 Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However,
20 immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

- 25 As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')₂ fragments) which are capable of specifically binding to protein. Fab and F(ab')₂ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library.
30 Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

Fusion Proteins

- 35 Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein

by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

5 Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

15 Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).)

25 Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D.

Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein.

Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

15 Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance

genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein

after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

5 In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and
10 which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al.,
15 Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entirety).

20

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes
25 known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention
30 can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic
35 cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this

technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

5 Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to
10 identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

15 There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type.
20 In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences
25 in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

30 Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et
35 al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay

(ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to

activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

5 Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

10 At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the
15 polypeptides of the present invention can be used to test the following biological activities.

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in
20 assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red
30 blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune
35 system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or

polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to:

- 5 blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, DiGeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

- 10 Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet
15 disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

- 20 A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the
25 present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

- Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia,
30 antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation,
35 Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

- 5 A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The
- 10 administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

- Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may
- 15 inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute
- 20 rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

- 25 A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

- 30 For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may
- 35 also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

15 **Infectious Disease**

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps,

Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

- 5 Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, 10 Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellacea Infections (e.g., Actinobacillus, 15 Heamophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae. Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, 20 respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases 25 (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

- Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not 30 limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, 35 giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide

of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

10 **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized

neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

5

Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial
10 cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to
15 treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

20 It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

25 **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples
30 of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology
35 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell
5 membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

10 The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations,
15 polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

20 Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The
25 molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which
30 bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if
35 a biological activity of the polypeptide has been altered.

Other Activities

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

- 5 A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

- 10 A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

- 15 A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

- Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

- Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

- Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
5 sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

10 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical
15 to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method
20 comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences
25 comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said
30 group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from
35 the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA

clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide
5 sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein
10 identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide
15 sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least
20 two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a
25 panel of at least two nucleotide sequences; wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the
30 deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

35 Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted

Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a

sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For

example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
5	Uni-Zap XR	pBluescript (pBS)
	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
10	pCMVSPORT 3.0	pCMVSPORT 3.0
	pCR [®] 2.1	pCR [®] 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the

phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 μg of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl_2 , 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation

at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X, according to the method described in Example 1. (See also, Sambrook.)

5 **Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system
10 (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or
15 human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to
20 standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of
25 conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is
30 determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified
35 using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA

sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalactopyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the

protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After
5 renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively
10 linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin
15 of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with *NdeI* and *XbaI*, *BamHI*, *XhoI*, or *Asp718*, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA
20 insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for *NdeI* (5' primer) and *XbaI*, *BamHI*, *XhoI*, or *Asp718* (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to
25 express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified,
30 all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount
35 of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50

mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

5 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel
10 electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μ g of a plasmid containing the polynucleotide is co-transfected with 1.0 μ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by
15 Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μ g of BaculoGold™ virus DNA and 5 μ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μ l Lipofectin plus 90 μ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection
20 mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

25 After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture
30 and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μ l of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in
35 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μ Ci of 35 S-methionine and 5 μ Ci 35 S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of

interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991);
5 Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

10 Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g.,
15 with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate
20 restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the
25 naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

30 The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

35 Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μ g of the expression plasmid pC6 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo

contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

15 Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

30 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated

by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

- 5 If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

10 GGGATCCGGAGCCCAAATCTTCTGACAAAACACACATGCCACCGTGCC
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACCC
CAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGT
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
15 AGCACGTACCGTGTGGTCAGCGTCTCACCCTCCTGCACCAGGACTGGCTG
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA
20 GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCCTGGACAAGAGCA
GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGC
GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

25

Example 10: Production of an Antibody from a Polypeptide

- The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera
30 containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

- In the most preferred method, the antibodies of the present invention are
35 monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J.

Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in
5 any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma
10 cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells
15 obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is
20 possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide.
25 Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')₂ and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such
30 fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use
35 "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies

- described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening Assays

- 10 The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.
- First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a
15 working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be
20 poly-lysine coated in advance for up to two weeks.
- Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.
- 25 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a
30 multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.
- 35 Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of

cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

- 5 While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄·5H₂O; 0.050 mg/L of Fe(NO₃)₃·9H₂O; 0.417 mg/L of FeSO₄·7H₂O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄·H₂O; 71.02 mg/L of Na₂HPO₄;
- 10 .4320 mg/L of ZnSO₄·7H₂O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml
- 15 of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of
- 25 Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122
- 30 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene
- 35 conical.

The transfection reaction is terminated, preferably by tag-tearing, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

- 5 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

10 It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

15 **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

20 GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

25 The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

30 The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two

groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- α , IFN- γ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a
5 WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

10 Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be
15 identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	IL-10	+	?	?	-	1,3	
	<u>gp130 family</u>						
10	IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	IL-11(Pleiotrophic)	?	+	?	?	1,3	
	OnM(Pleiotrophic)	?	+	+	?	1,3	
	LIF(Pleiotrophic)	?	+	+	?	1,3	
	CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrophic)	?	+	?	?	1,3	
	IL-12(Pleiotrophic)	+	-	+	+	1,3	
	<u>g-C family</u>						
20	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
25	<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS
30	<u>Growth hormone family</u>						
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
35	<u>Receptor Tyrosine Kinases</u>						
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
40	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:
 5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCG
 AAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:
 5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATG
 ATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCCGCC
 CTAAGTCCGCCCATCCCGCCCCTAAGTCCGCCCAGTTCCGCCCATTCTCCGC
 CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGC
 CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTT
 TGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final
5 concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

10 On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

15 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12
20 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples
25 from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

30 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells.

- 5 Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

- 10 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

- 15 Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 1 mM MgCl_2 , and 675 uM CaCl_2 . Incubate at 37°C for 45 min.

- 20 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

- 25 These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

- 30 Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

- 5 The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

- 10 Add 200 μ l of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 μ l supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ μ l of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

15

Example 16: High-Throughput Screening Assay for T-cell Activity

- 20 NF- κ B (Nuclear Factor κ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- κ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- κ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

- 25 In non-stimulated conditions, NF- κ B is retained in the cytoplasm with I- κ B (Inhibitor κ B). However, upon stimulation, I- κ B is phosphorylated and degraded, causing NF- κ B to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- κ B include IL-2, IL-6, GM-CSF, ICAM-1 and class I MHC.

- 30 Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- κ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- κ B would be useful in treating

diseases. For example, inhibitors of NF- κ B could be used to treat those diseases related to the acute or chronic activation of NF- κ B, such as rheumatoid arthritis.

To construct a vector containing the NF- κ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- κ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:
5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)
Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCCTAACTCCGCCCA
TCCCGCCCCCTAACTCCGCCCCAGTTCCGCCCATTTCTCCGCCCCATGGCTGACT
AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTC
CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:
3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2- promoter plasmid (Clontech) with this NF- κ B/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- κ B/SV40/SEAP cassette is removed from the above NF- κ B/SEAP vector using restriction enzymes Sall and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF- κ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with Sall and NotI.

Once NF- κ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 μ l of 2.5x dilution buffer into Optiplates containing 35 μ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 μ l Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 μ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6

23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours.

The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

5 A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10⁶ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.
10 The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10⁶ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4.
15 The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular
20 signaling event which has resulted in an increase in the intracellular Ca⁺⁺ concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

25 The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is
30 unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor
35 associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members

of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and
5 PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride,
10 pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM
15 EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-
20 POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the
25 absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying 30 **Phosphorylation Activity**

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine
35 phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase,

Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with



specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

5 The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

10 Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

15 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

20 **Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's

solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

5 The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, 10 such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

15 The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. 20 Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for 25 example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

30 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of 35 manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long
5 terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set
10 forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to
15 transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is
20 then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media,
25 containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is
30 required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and

connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization,

and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 28: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into

enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

5 The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al.
10 (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to
15 be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that
20 cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant
25 gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue
30 samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or
35 crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines

in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening
5 of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides
10 of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 29: Knock-Out Animals.

15 Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide
20 of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate
25 knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson
30 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to
35 express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*,

animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

10 The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or

15 intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and

20 Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the

25 cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders

30 associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

It will be clear that the invention may be practiced otherwise than as particularly

35 described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing
5 submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>76</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 29 January 1998	Accession Number 209603
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only
<input checked="" type="checkbox"/> This sheet was received with the international application
Authorized officer <i>Hal Saunders</i>

For International Bureau use only
<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

- (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

- (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
- (b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

WO 99/40100

PCT/US99/02293

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<210> 15
 <211> 815
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (406)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (794)
 <223> n equals a,t,g, or c

<400> 15						
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tgtcttcttc	ttcttcttct	tcttcttctt	cttcttcttt	ggtccttaag	tgaaataaag	180
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tgtaccgaca	gaaatagaca	tttcatcatg	taaaattcct	gttattctgg	aaaaacctat	540
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accctatcct	gttattttaa	tgtgaacatt	tattgtacat	tcagtgaagt	atagtggttaa	720
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<210> 16
 <211> 990
 <212> DNA
 <213> Homo sapiens

<400> 16						
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WO 99/40100

PCT/US99/02293

acggggaccct	gcagctgggc	caggccctca	acgggtgtgta	caggaccacg	gagggacggc	180
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tggaggagga	tattctgcag	ctgcaggcag	aggccacagc	tgaggtgctg	ggggaggtgg	360
cccaggcaca	gaaggtgcta	cgggacagcg	tkcagcggct	agaagtccag	ytragragcg	420
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<210> 17

<211> 1188

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (892)

<223> n equals a,t,g, or c

<400> 17

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ccccgcaccc	cagcaggcgg	ctcccgcggg	cgccggctcc	cggctacgaa	gcgaggaacg	180
agcgggcggc	gggcacgagg	cagctctgga	cggatcaatg	caagccagac	gatgaccagt	240
tgtggccagc	agtccttgaa	cgtgctcgcc	gtcctcttct	cattgctggt	ttctgcagtc	300
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aacacgggtc	tcaaatactg	ctgcaacgag	acggagttcc	aggcgggtgat	gcaggcgaaac	480
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<210> 18

<211> 1605

<212> DNA

<213> Homo sapiens

<400> 18

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aatgacaact	tcattttcac	atgttactca	gttcccta	aggatgggtg	tcctttgttg	120

aacctgtatt	gatttttttt	tttttaacta	tattgattcg	tttactagaa	cagtcctaatt	180
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gaattgtaaa	taaatatatc	agttttttty	cccttcggtc	ttccacagca	gtattattgt	1440
ctttgtggag	ttgactaatg	ataatttaaa	aatcctgtaa	tggttttcta	ctaaaataag	1500
gtcatagtgg	catataccaa	ataaaatcaa	atacagaaat	acaaaaaaaa	aaaaaaaaaa	1560
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<210> 19

<211> 2089

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (774)

<223> n equals a,t,g, or c

<400> 19

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gccctggctg	cagagtgttg	aggcgaatca	ttcacttcaa	cattccaaac	wcaatcacca	660
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gcagccactt	atcttggcta	aatagaacct	cacctgctca	tgaccagaga	gcatttagga	1980
taatagagga	cctaactgaa	ggaatccttg	tatatgaaag	gagttatttt	agaaaagcaa	2040
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<210> 20

<211> 1281

<212> DNA

<213> Homo sapiens

<400> 20

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cagcctgggt	aatatagctg	ctgctggaag	tgacgagaag	tgcaagctgg	cgatgcagag	180
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aacgagaaca	gcaagtgggt	gggtgaaaag	gaatagaagc	agagaaaatc	aggaaatgct	300
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catactgggc	tacagaatac	ttatgcattt	ttgtagttaa	tttaaaatc	tctaaagagg	1200
caatgtgtta	aaggaatcct	aaagtaagtc	ttgtataaaa	gcaaatggtc	cttccctcaa	1260
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<210> 21

<211> 1761

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1207)

<223> n equals a,t,g, or c

<400> 21

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<210> 22

<211> 1189

<212> DNA

<213> Homo sapiens

<400> 22

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<211> 1608
<212> DNA
<213> Homo sapiens
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<400> 24

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<210> 25

<211> 1964

<212> DNA

<213> Homo sapiens

<400> 25

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<211> 933

<212> DNA

<213> Homo sapiens

<400> 26

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<210> 27

<211> 1237

<212> DNA

<213> Homo sapiens

<220>

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<222> (556)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (619)

<223> n equals a,t,g, or c.

<220>

<221> SITE

<222> (672)

<223> n equals a,t,g, or c

<400> 27

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WO 99/40100

PCT/US99/02293

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<211> 960

<212> DNA

<213> Homo sapiens

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<211> 1067

<212> DNA

<213> Homo sapiens

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<210> 30

<211> 1063

<212> DNA

<213> Homo sapiens

<220>

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<222> (965)

<223> n equals a,t,g, or c

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<211> 1430

<212> DNA

<213> Homo sapiens

<400> 31

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 <212> DNA
 <213> Homo sapiens

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 <222> (1339)
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<210> 33
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 <212> DNA
 <213> Homo sapiens

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<211> 727

<212> DNA

<213> Homo sapiens

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<210> 35

<211> 1991

<212> DNA

<213> Homo sapiens

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<222> (300)

<223> n equals a,t,g, or c

<220>

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<222> (353)

<223> n equals a,t,g, or c

<400> 35

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 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (880)
 <223> n equals a,t,g, or c

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<211> 1558

<212> DNA

<213> Homo sapiens

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PCT/US99/02293

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 <212> DNA
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<211> 1280

<212> DNA

<213> Homo sapiens

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<210> 41

<211> 1918

<212> DNA

<213> Homo sapiens

<400> 41

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<210> 42

<211> 1268

<212> DNA

<213> Homo sapiens

<220>

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<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (15)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (23)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (368)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (479)

<223> n equals a,t,g, or c

<400> 42

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aactcgta						1268

<210> 43

<211> 1201

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1192)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1197)

<223> n equals a,t,g, or c

<400> 43

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gaataatagg	attgctttga	ggatcaaata	agttataaaa	ccacttagaa	cagtgttcaa	240
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gccagaggtc	ggattcatgt	ggcaggatgg	ggccaaaact	gtacaaaagc	ttggagatga	480
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WO 99/40100

PCT/US99/02293

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<210> 44

<211> 819

<212> DNA

<213> Homo sapiens

<400> 44

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<210> 45

<211> 1566

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (16)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (170)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (184)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (728)

<223> n equals a,t,g, or c

<400> 45

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<210> 46

<211> 2094

<212> DNA

<213> Homo sapiens

<400> 46

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<210> 47

<211> 956

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (319)

<223> n equals a,t,g, or c

<400> 47

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<210> 48

<211> 1715

<212> DNA

<213> Homo sapiens

<400> 48

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<210> 49

<211> 1461

<212> DNA

<213> Homo sapiens

<400> 49

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<210> 50

<211> 1238

<212> DNA

<213> Homo sapiens

<400> 50

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<210> 51

<211> 2581

<212> DNA

<213> Homo sapiens

<400> 51

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<210> 52

<211> 991

<212> DNA

<213> Homo sapiens

<400> 52

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<210> 53
 <211> 2422
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (388)
 <223> n equals a,t,g, or c

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<210> 54
 <211> 985
 <212> DNA

<213> Homo sapiens

<400> 54

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<210> 55

<211> 1764

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1314)

<223> n equals a,t,g, or c

<400> 55

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<210> 56
 <211> 932
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (888)
 <223> n equals a,t,g, or c

<220>
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 <222> (890)
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<220>
 <221> SITE
 <222> (892)
 <223> n equals a,t,g, or c

<400> 56	
aattcggcac	gaggagcadc
ggttggtgtg	ctcatggcag
tcgtcaccgc	aagatgaagc
ccatgggtccc	ggggccaccg
gccatgccac	caaccctgct
ctgggcatgg	acgaggtcaa
ctgctctttc	tgctcctctg
aaagcctgtg	ctgtgccccca
gctgccgtca	acccaattgt
actcaygccc	cctgctgggg
gtgaagcagg	ctggtaggca
acagcaaggg	aggggtaggg
cctcgaacca	cctgtaatct
cgagggactg	ggaaagaggc
ccacttctac	aatctcattc
tcagaagtga	caattcaaaa
	aaaaaaaaaa
	aa
	60
	120
	180
	240
	300
	360
	420
	480
	540
	600
	660
	720
	780
	840
	900
	932

<210> 57
 <211> 957
 <212> DNA
 <213> Homo sapiens

<400> 57	
gcattttctgc	tcctgatctg
actgatgctt	gtraaacagt
gaactctgca	gcccagctt
gcctcccagt	ggcagccaca
cacgctctga	gtccttgccc
gccagatcca	aggcacaggg
	ccctgctgca
	tggtccaca
	tggaagtctg
	agtccccgt
	60
	120
	180
	240
	300
	360

gtccagccgc	cggccctgca	ggtgcccagc	agctctgaca	aagcggggca	gggcccgtgg	420
ggtgtccctg	gacagcgggg	cctgggtggc	aggggaggag	gctgcaagg	gacaccag	480
ttgccttgca	gacgtacgga	gcgcaagagg	acggcagcgt	cggcgaagg	gacctgtcct	540
gcatcctcaa	gacggccctg	ggggtggcag	agctcaccgt	gaccgacct	ttccgagcca	600
ttgaccaaga	ggagaagggg	aagatcacat	tcggtgagcc	cgcaggagtg	gggtcgtcct	660
cgcgaccctt	gggcgggggc	tgggcagagt	gtggggcgag	tctccgtggg	agcccaggac	720
aggagtggag	tccccgccat	gcctccattc	accaggctgc	cctgtgtaac	aaagaaaccc	780
ctgagaagga	aggttctgga	gacctggcag	ggttcgtagg	gagctttcca	atctgatttg	840
ttttggcgat	ttatacaacc	aaactccaag	cccagttccg	aagctctgag	ccttccatgg	900
cctcaggctg	ggattcaggt	gcctggaggt	gggggatacc	cgcacccagc	cctcgag	957

<210> 58

<211> 1433

<212> DNA

<213> Homo sapiens

<400> 58

ggcagagcac	ttatgtkttt	ggcattctcc	gtcatcattc	tggccggggc	gggcagttct	60
aggagtggga	actcagtcct	ggtggaaaag	gaagtcgtgg	agggagggct	agggccgtgg	120
gggaactgct	ctgctgagcc	tcttctcac	ctgctgcttc	ctaggactaa	cctgaaggct	180
aaggtaccag	gctgaagtc	gtgctcagaa	aaccaatcgt	cattctttgg	ggtttttttt	240
cttgaagagc	cactttctct	ttacctgtt	ctagcctgtt	ggaggtaggg	tttctgcaat	300
tccaaaggcc	gtacacagcc	tctcaccatc	agaccacttt	ttaaggctct	tcgttcatac	360
ctagctcgaa	gattcacttc	ctcaggaagc	catttttagt	acaaatctgg	gaaaaactaa	420
aatgctttca	ttgtgccatg	ttttctgttg	cagcttcagt	accgtacct	gtggtcaggg	480
atacttacaa	gtttcttttt	acagtaaccc	cttgtggaca	tctaataaat	ggtcattatt	540
tttttagtact	agtttgtttt	cctgaacact	gtaagatctg	tgactgacgt	ttgatacctt	600
aaagcagtg	catataataa	ctaccacta	tttgttcttt	atttctgtca	gataaaaatg	660
ttctatgtag	tgtctacagt	catttttttt	ttaactagaa	tttagatttg	gaagtagttt	720
ttctattagt	tgatttgc	gaaatacaaa	attaggaaaa	ggcttattcc	acctcaacct	780
agttgaacta	ttaatgattt	tttttttttt	ttgaggattt	gggctctttc	tagatagaaa	840
atcacccctga	acttctagct	ttgcattgtg	aagtgcagct	catgaagatg	agaaaatggt	900
gggagatcat	ttttgcaaag	ggcataatag	tcggcattca	gatatgagtt	aactgcagag	960
ggaaaattgc	aagctgtcat	gttggccttg	ttcctctcaa	ccttctggta	acctaaccaag	1020
tcctacagg	ttgtatgtga	aattgcaaga	tgattatata	gccctgttga	atttacaacc	1080
agatcttgct	ttcaaaccat	tattagccaa	gggttttgatt	ccacacctgt	gttcatggat	1140
tttttggtat	tagacattgc	tgtaactctg	ttttcacttt	ttcatctgtt	atcttggtct	1200
acttaagggg	gaagggtatca	gcagcctagg	accacttggt	ttctgttttt	atgtttcata	1260
gttcatggct	gataaaaatt	acctgtcctt	aggccgagtg	cagtgcctca	cacctgtaat	1320
cccagcactt	tgggagggcg	aggtgagtag	atcacctgag	atcaggagtt	cgagaccagc	1380
ctggacaaca	agagcaaaac	tccatctcca	aaaaaaaaaa	aaaaaaaaact	cga	1433

<210> 59

<211> 1940

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1573)

<223> n equals a,t,g, or c

<400> 59

tcganccacg	cgctccgagg	cgctgggggc	aacaaagcct	tctacttgag	cagtttttcc	60
atcactgata	tgtgcaggaa	atgaagacat	tgcctgccat	gcttggaact	gggaaattat	120
tttgggtctt	cttcttaatc	ccatatctgg	acatctggaa	catccatggg	aaagaatcat	180
gtgatgtaca	gctttatata	aagagacaat	ctgaacactc	catcttagca	ggagatccct	240
ttgaactaga	atgccctgtg	aaatactgtg	ctaacaggcc	tcattgtgact	tggtgcaagc	300
tcaatggaac	aacatgtgta	aaacttgaag	atagacaaac	aagttggaag	aagagaagaa	360
catttcattt	ttcatctacr	ytttgaacca	gtgcttccta	atgacaatgg	gtcataccgc	420
tgttctgcaa	attttcagtc	taatctcatt	gaaagccact	caacaactct	ttatgtgaca	480
gggtgagttc	caacacctag	accatctgat	atttttctta	taatgtttcc	aggaagaggg	540
gggttcagtt	tctcaagtga	ttatgttaga	aagccaactc	ctatagcaca	tctgaaatct	600
gctacacctc	acagattggt	atgtgccagt	gtgtacatat	gtgtgtgtat	gtgtgcgttt	660
gargtgagtg	agatagagga	gagtagakaa	atagatagta	aaagtatttg	tttttgactt	720
tagggattat	aaaatttatt	tgataagtcc	aaaagttagc	cactgaaata	ttgaaaaaat	780
tataaagtga	atacctatag	ttgcgaatag	ctctgtgatt	gcttgtcctt	ctttgttggt	840
tttttttctt	ctttttccca	tttttctott	ctttactttt	gttcattaca	atttcttgaa	900
gttatgtttg	tggtgcttag	gcaattaaac	acttcttaac	agttcacagt	ttgttttagag	960
gaaaaacagc	aaacaactaa	ctgacttcct	agtgttttct	tgggaatatt	cagagyttca	1020
tctytyttcc	ctgttccccc	aaagaggcct	ttaatatgct	ttgacaactg	aggaaggaca	1080
gatagaagtt	aagcttgagg	aaaccaagct	gaataaaaca	tgaaaaaata	catagggggg	1140
gagtaggtaa	gagtaaaaaa	tacttggttt	ataaaaattt	tatagccaac	atcatattca	1200
atgggtgaaag	gcttagagct	ttccccctaa	gaacaggaac	aagacatgga	tccttgcttt	1260
tgccatttcc	atttaacatt	aaactgaaaa	ttctagccag	agcaaacagg	caagaacaag	1320
aaataaaaaga	tatctaactt	agaaaaaaag	aagtaaaact	ttattcacag	atggcatgaa	1380
cttatgtgta	gaaaaattct	taaaaatttg	tttaaaacta	ttaaagctaa	tacatgaatt	1440
tagcaattcc	acatgatata	ggatcaacac	acmaaaatca	gtgatatttc	tatacactag	1500
caataaaaca	tccacaaaga	aaattaagga	aacagttcca	tttacaatag	catcaaaatg	1560
aataaaaatat	ttnagtacaa	atttaaccac	agaggtataa	gagttgtaca	ctgaacaaag	1620
aaagcatggc	tgaaagaaat	tcaagaatat	gtaaaataat	gcaaagacat	tctgtattca	1680
tggactgaaa	gatgtaatat	tgtaaagata	gcaatattcc	ccaaggtgat	ctacagattc	1740
aatgcagttc	cactaaaatc	ctaacagctt	tttgttgcta	ttgcagaaat	aaaaaagctg	1800
atcctaaaat	tcacattgag	ttgcaacaga	cccagaattg	ccaaaacaat	cttgaaaaag	1860
aacaaaactg	aagctaagac	ttccctattt	caaaacttac	tacaaaatga	cagttaaaaa	1920
aaaaaaaaaa	gggcggccgc					1940

<210> 60

<211> 308

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (165)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (247)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (308)

<223> Xaa equals stop translation

<400> 60

Met Gly Thr Gln Glu Gly Trp Cys Leu Leu Leu Cys Leu Ala Leu Ser
 1 5 10 15
 Gly Ala Ala Glu Thr Lys Pro His Pro Ala Glu Gly Gln Trp Arg Ala
 20 25 30
 Val Asp Val Val Leu Asp Cys Phe Leu Ala Lys Asp Gly Ala His Arg
 35 40 45
 Gly Ala Leu Ala Ser Ser Glu Asp Arg Ala Arg Ala Ser Leu Val Leu
 50 55 60
 Lys Gln Val Pro Val Leu Asp Asp Gly Ser Leu Glu Asp Phe Thr Asp
 65 70 75 80
 Phe Gln Gly Gly Thr Leu Ala Gln Asp Asp Pro Pro Ile Ile Phe Glu
 85 90 95
 Ala Ser Val Asp Leu Val Gln Ile Pro Gln Ala Glu Ala Leu Leu His
 100 105 110
 Ala Asp Cys Ser Gly Lys Glu Val Thr Cys Glu Ile Ser Arg Tyr Phe
 115 120 125
 Leu Gln Met Thr Glu Thr Thr Val Lys Thr Ala Ala Trp Phe Met Ala
 130 135 140
 Asn Met Gln Val Ser Gly Gly Gly Pro Ser Ile Ser Leu Val Met Lys
 145 150 155 160
 Thr Pro Arg Val Xaa Lys Asn Glu Ala Leu Trp His Pro Thr Leu Asn
 165 170 175
 Leu Pro Leu Ser Pro Gln Gly Thr Val Arg Thr Ala Val Glu Phe Gln
 180 185 190
 Val Met Thr Gln Thr Gln Ser Leu Ser Phe Leu Leu Gly Ser Ser Ala
 195 200 205
 Ser Leu Asp Cys Gly Phe Ser Met Ala Pro Gly Leu Asp Leu Ile Ser
 210 215 220
 Val Glu Trp Arg Leu Gln His Lys Gly Arg Gly Gln Leu Val Tyr Ser
 225 230 235 240
 Trp Thr Ala Gly Arg Gly Xaa Leu Cys Gly Arg Ala Leu Pro Trp Ser
 245 250 255
 Leu His Asn Trp Ala Trp Pro Gly Met Pro Pro Ser Pro Cys Pro Ala
 260 265 270
 Ser Leu Tyr Arg Thr Arg Gly Pro Thr Phe Ala Arg Ser Pro Pro Leu
 275 280 285
 Cys Thr Glu Leu Ser Arg Ser Ser Ser Ser Thr Ser Lys Leu Pro Leu
 290 295 300
 Lys Tyr Asp Xaa

305

<210> 61
 <211> 579
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (64)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (574)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (579)
 <223> Xaa equals stop translation

<400> 61
 Met Arg Ala Ala Arg Ala Ala Pro Leu Leu Gln Leu Leu Leu Leu Leu
 1 5 10 15
 Gly Pro Trp Leu Glu Ala Ala Gly Val Ala Glu Ser Pro Leu Pro Ala
 20 25 30
 Val Val Leu Ala Ile Leu Ala Arg Asn Ala Glu His Ser Leu Pro His
 35 40 45
 Tyr Leu Gly Ala Leu Glu Arg Leu Asp Tyr Pro Arg Ala Arg Met Xaa
 50 55 60
 Leu Trp Cys Ala Thr Asp His Asn Val Asp Asn Thr Thr Glu Met Leu
 65 70 75 80
 Gln Glu Trp Leu Ala Ala Val Gly Asp Asp Tyr Ala Ala Val Val Trp
 85 90 95
 Arg Pro Glu Gly Glu Pro Arg Phe Tyr Pro Asp Glu Glu Gly Pro Lys
 100 105 110
 His Trp Thr Lys Glu Arg His Gln Phe Leu Met Glu Leu Lys Gln Glu
 115 120 125
 Ala Leu Thr Phe Ala Arg Asn Trp Gly Ala Asp Tyr Ile Leu Phe Ala
 130 135 140
 Asp Thr Asp Asn Ile Leu Thr Asn Asn Gln Thr Leu Arg Leu Leu Met
 145 150 155 160
 Gly Gln Gly Leu Pro Val Val Ala Pro Met Leu Asp Ser Gln Thr Tyr
 165 170 175
 Tyr Ser Asn Phe Trp Cys Gly Ile Thr Pro Gln Gly Tyr Tyr Arg Arg

180	185	190
Thr Ala Glu Tyr Phe Pro Thr Lys Asn Arg Gln Arg Arg Gly Cys Phe 195 200 205		
Arg Val Pro Met Val His Ser Thr Phe Leu Ala Ser Leu Arg Ala Glu 210 215 220		
Gly Ala Asp Gln Leu Ala Phe Tyr Pro Pro His Pro Asn Tyr Thr Trp 225 230 235 240		
Pro Phe Asp Asp Ile Ile Val Phe Ala Tyr Ala Cys Gln Ala Ala Gly 245 250 255		
Val Ser Val His Val Cys Asn Glu His Arg Tyr Gly Tyr Met Asn Val 260 265 270		
Pro Val Lys Ser His Gln Gly Leu Glu Asp Glu Arg Val Asn Phe Ile 275 280 285		
His Leu Ile Leu Glu Ala Leu Val Asp Gly Pro Arg Met Gln Ala Ser 290 295 300		
Ala His Val Thr Arg Pro Ser Lys Arg Pro Ser Lys Ile Gly Phe Asp 305 310 315 320		
Glu Val Phe Val Ile Ser Leu Ala Arg Arg Pro Asp Arg Arg Glu Arg 325 330 335		
Met Leu Ala Ser Leu Trp Glu Met Glu Ile Ser Gly Arg Val Val Asp 340 345 350		
Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly 355 360 365		
Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu 370 375 380		
Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu 385 390 395 400		
Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp 405 410 415		
Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu 420 425 430		
Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg 435 440 445		
Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly 450 455 460		
Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg 465 470 475 480		
Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met 485 490 495		

Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
 500 505 510
 Glu Gln Tyr Lys Ala His Phe Trp Pro Arg Asp Leu Val Ala Phe Ser
 515 520 525
 Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
 530 535 540
 Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Asp Ser Gly
 545 550 555 560
 Arg Leu Ile Ser Trp Ser Gly Ser Gln Lys Thr Leu Arg Xaa Pro Ala
 565 570 575
 Trp Thr Xaa

<210> 62
 <211> 184
 <212> PRT
 <213> Homo sapiens

<400> 62
 Met Leu Met Leu Ala Val Leu Met Ala Ala Thr His Ala Val Tyr Gly
 1 5 10 15
 Lys Leu Leu Leu Phe Glu Tyr Arg His Arg Lys Met Lys Pro Val Gln
 20 25 30
 Met Val Pro Ala Ile Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala
 35 40 45
 Thr Gly Gln Ala Ala Ala Asn Trp Ile Ala Gly Phe Gly Arg Gly Pro
 50 55 60
 Met Pro Pro Thr Leu Leu Gly Ile Arg Gln Asn Gly His Ala Ala Ser
 65 70 75 80
 Arg Arg Leu Leu Gly Met Asp Glu Val Lys Gly Glu Lys Gln Leu Gly
 85 90 95
 Arg Met Phe Tyr Ala Ile Thr Leu Leu Phe Leu Leu Leu Trp Ser Pro
 100 105 110
 Tyr Ile Val Ala Cys Tyr Trp Arg Val Phe Val Lys Ala Cys Ala Val
 115 120 125
 Pro His Arg Tyr Leu Ala Thr Ala Val Trp Met Ser Phe Ala Gln Ala
 130 135 140
 Ala Val Asn Pro Ile Val Cys Phe Leu Leu Asn Lys Asp Leu Lys Lys
 145 150 155 160
 Cys Leu Arg Thr His Ala Pro Cys Trp Gly Thr Gly Gly Ala Pro Ala
 165 170 175

Pro Arg Glu Pro Tyr Cys Val Met
180

<210> 63

<211> 306

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (306)

<223> Xaa equals stop translation

<400> 63

Met Gly Ile Leu Leu Gly Leu Leu Leu Leu Gly His Leu Thr Val Asp
1 5 10 15

Thr Tyr Gly Arg Pro Ile Leu Glu Val Pro Glu Ser Val Thr Gly Pro
20 25 30

Trp Lys Gly Asp Val Asn Leu Pro Cys Thr Tyr Asp Pro Leu Gln Gly
35 40 45

Tyr Thr Gln Val Leu Val Lys Trp Leu Val Gln Arg Gly Ser Asp Pro
50 55 60

Val Thr Ile Phe Leu Arg Asp Ser Ser Gly Asp His Ile Gln Gln Ala
65 70 75 80

Lys Tyr Gln Gly Arg Leu His Val Ser His Lys Val Pro Gly Asp Val
85 90 95

Ser Leu Gln Leu Ser Thr Leu Glu Met Asp Asp Arg Ser His Tyr Thr
100 105 110

Cys Glu Val Thr Trp Gln Thr Pro Asp Gly Asn Gln Val Val Arg Asp
115 120 125

Lys Ile Thr Glu Leu Arg Val Gln Lys His Ser Ser Lys Leu Leu Lys
130 135 140

Thr Lys Thr Glu Ala Pro Thr Thr Met Thr Tyr Pro Leu Lys Ala Thr
145 150 155 160

Ser Thr Val Lys Gln Ser Trp Asp Trp Thr Thr Asp Met Asp Gly Tyr
165 170 175

Leu Gly Glu Thr Ser Ala Gly Pro Gly Lys Ser Leu Pro Val Phe Ala
180 185 190

Ile Ile Leu Ile Ile Ser Leu Cys Cys Met Val Val Phe Thr Met Ala
195 200 205

Tyr Ile Met Leu Cys Arg Lys Thr Ser Gln Gln Glu His Val Tyr Glu
210 215 220

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Ala Ala Arg Ala His Ala Arg Glu Ala Asn Asp Ser Gly Glu Thr Met
 225 230 235 240

Arg Val Ala Ile Phe Ala Ser Gly Cys Ser Ser Asp Glu Pro Thr Ser
 245 250 255

Gln Asn Leu Gly Asn Asn Tyr Ser Asp Glu Pro Cys Ile Gly Gln Glu
 260 265 270

Tyr Gln Ile Ile Ala Gln Ile Asn Gly Asn Tyr Ala Arg Leu Leu Asp
 275 280 285

Thr Val Pro Leu Asp Tyr Glu Phe Leu Ala Thr Glu Gly Lys Ser Val
 290 295 300

Cys Xaa
 305

<210> 64
 <211> 108
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (9)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (13)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (95)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (108)
 <223> Xaa equals stop translation

<400> 64
 Met Ala Val Val Leu Ser Xaa Lys Xaa His Arg Gly Xaa Tyr Cys Gly
 1 5 10 15

Arg Thr Ser Leu Leu Ser Leu Leu Ser Cys Leu Leu Leu Leu
 20 25 30

Leu Leu Leu Leu Leu Leu Trp Ser Leu Ser Glu Ile Lys Thr Leu
 35 40 45

Lys Leu Ile Cys Ile Leu Ser Ala Arg Asp Ala Asp Gly Ser Arg Ala
50 55 60

Lys Ser His Gly Phe Gln Ile Arg Tyr Ser Ala His Ser Phe Gln Gly
65 70 75 80

His Arg Phe Leu Lys Gly Pro Gly Phe Glu Glu Met Ala Asn Xaa Glu
85 90 95

Pro Ser Glu Asn Leu Ile Trp Lys Thr Cys Met Xaa
100 105

<210> 65

<211> 191

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (191)

<223> Xaa equals stop translation

<400> 65

Met Pro Val Pro Thr Leu Cys Leu Leu Trp Ala Leu Ala Met Val Thr
1 5 10 15

Arg Pro Ala Ser Ala Ala Pro Met Xaa Gly Pro Glu Leu Ala Gln His
20 25 30

Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala
35 40 45

Leu Asn Gly Val Tyr Arg Thr Glu Gly Arg Leu Thr Lys Ala Arg
50 55 60

Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu
65 70 75 80

Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu
85 90 95

Glu Thr Gln Met Glu Glu Asp Ile Leu Gln Leu Gln Ala Glu Ala Thr
100 105 110

Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp
115 120 125

Ser Val Gln Arg Leu Glu Val Gln Leu Arg Ser Ala Trp Leu Gly Pro
130 135 140

Ala Tyr Arg Glu Phe Glu Val Leu Lys Ala His Ala Asp Lys Gln Glu

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145	150	155	160
Pro Thr Ser Tyr Gly	Pro His Arg Pro Arg Gln Arg Gln Arg Arg Glu		
	165	170	175
Met Val Ala Gln Gln His Arg Leu Arg Gln Ile Gln Glu Arg Xaa			
	180	185	190

<210> 66
 <211> 200
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (118)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (120)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (200)
 <223> Xaa equals stop translation

<400> 66
 Met Thr Ser Cys Gly Gln Gln Ser Leu Asn Val Leu Ala Val Leu Phe
 1 5 10 15
 Ser Leu Leu Phe Ser Ala Val Leu Ser Ala His Phe Arg Val Cys Glu
 20 25 30
 Pro Tyr Thr Asp His Lys Gly Arg Tyr His Phe Gly Phe His Cys Pro
 35 40 45
 Arg Leu Ser Asp Asn Lys Thr Phe Ile Leu Cys Cys His His Asn Asn
 50 55 60
 Thr Val Phe Lys Tyr Cys Cys Asn Glu Thr Glu Phe Gln Ala Val Met
 65 70 75 80
 Gln Ala Asn Leu Thr Ala Ser Ser Glu Gly Tyr Met His Asn Asn Tyr
 85 90 95
 Thr Ala Leu Leu Gly Val Trp Ile Tyr Gly Phe Phe Val Leu Met Leu
 100 105 110
 Leu Val Leu Asp Leu Xaa Tyr Xaa Ser Ala Met Asn Tyr Asp Ile Cys
 115 120 125
 Lys Val Tyr Leu Ala Arg Trp Gly Ile Gln Gly Arg Trp Met Lys Gln
 130 135 140
 Asp Pro Arg Arg Trp Gly Asn Pro Ala Arg Ala Pro Arg Pro Gly Gln

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<210> 67
<211> 62
<212> PRT
<213> Homo sapiens
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```
<220>
<221> SITE
<222> (62)
<223> Xaa equals stop translation
```

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<400> 67
Met Leu Leu Ser Ser Leu Ile Gly Trp Cys Ser Phe Val Glu Pro Val
  1                      5                      10                      15

Leu Ile Phe Phe Phe Leu Thr Ile Leu Ile Arg Leu Leu Glu Gln Ser
                20                      25                      30

Asn Trp Gly Ile Glu Glu Met Lys Thr Gly Tyr Phe Cys Ile Cys Glu
          35                      40                      45

Val Gly Thr Gly Asn Ile Trp Thr Cys Ser Ser Tyr Ser Xaa
    50                      55                      60

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<210> 68
<211> 608
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (242)
<223> Xaa equals any of the naturally occurring L-amino acids
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```
<220>
<221> SITE
<222> (608)
<223> Xaa equals stop translation
```

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<400> 68
Met Arg Thr Pro Gln Leu Ala Leu Leu Gln Val Phe Phe Leu Val Phe
 1             5             10             15
Pro Asp Gly Val Arg Pro Gln Pro Ser Ser Pro Ser Gly Ala Val
      20             25             30

```

Pro Thr Ser Leu Glu Leu Gln Arg Gly Thr Asp Gly Gly Thr Leu Gln
 35 40 45
 Ser Pro Ser Glu Ala Thr Ala Thr Arg Pro Ala Val Pro Gly Leu Pro
 50 55 60
 Thr Val Val Pro Thr Leu Val Thr Pro Ser Ala Pro Gly Asn Arg Thr
 65 70 75 80
 Val Asp Leu Phe Pro Val Leu Pro Ile Cys Val Cys Asp Leu Thr Pro
 85 90 95
 Gly Ala Cys Asp Ile Asn Cys Cys Cys Asp Arg Asp Cys Tyr Leu Leu
 100 105 110
 His Pro Arg Thr Val Phe Ser Phe Cys Leu Pro Gly Ser Val Arg Ser
 115 120 125
 Ser Ser Trp Val Cys Val Asp Asn Ser Val Ile Phe Arg Ser Asn Ser
 130 135 140
 Pro Phe Pro Ser Arg Val Phe Met Asp Ser Asn Gly Ile Arg Gln Phe
 145 150 155 160
 Cys Val His Val Asn Asn Ser Asn Leu Asn Tyr Phe Gln Lys Leu Gln
 165 170 175
 Lys Val Asn Ala Thr Asn Phe Gln Ala Leu Ala Ala Glu Phe Gly Gly
 180 185 190
 Glu Ser Phe Thr Ser Thr Phe Gln Thr Gln Ser Pro Pro Ser Phe Tyr
 195 200 205
 Arg Ala Gly Asp Pro Ile Leu Thr Tyr Phe Pro Lys Trp Ser Val Ile
 210 215 220
 Ser Leu Leu Arg Gln Pro Ala Gly Val Gly Ala Gly Gly Leu Cys Ala
 225 230 235 240
 Glu Xaa Asn Pro Ala Gly Phe Leu Glu Ser Lys Ser Thr Thr Cys Thr
 245 250 255
 Arg Phe Phe Lys Asn Leu Ala Ser Ser Cys Thr Leu Asp Ser Ala Leu
 260 265 270
 Asn Ala Ala Ser Tyr Tyr Asn Phe Thr Val Leu Lys Val Pro Arg Ser
 275 280 285
 Met Thr Asp Pro Gln Asn Met Glu Phe Gln Val Pro Val Ile Leu Thr
 290 295 300
 Ser Gln Ala Asn Ala Pro Leu Leu Ala Gly Asn Thr Cys Gln Asn Val
 305 310 315 320
 Val Ser Gln Val Thr Tyr Glu Ile Glu Thr Asn Gly Thr Phe Gly Ile
 325 330 335
 Gln Lys Val Ser Val Ser Leu Gly Gln Thr Asn Leu Thr Val Glu Pro

340	345	350
Gly Ala Ser Leu Gln Gln His Phe Ile Leu Arg Phe Arg Ala Phe Gln		
355	360	365
Gln Ser Thr Ala Ala Ser Leu Thr Ser Pro Arg Ser Gly Asn Pro Gly		
370	375	380
Tyr Ile Val Gly Lys Pro Leu Leu Ala Leu Thr Asp Asp Ile Ser Tyr		
385	390	395
Ser Met Thr Leu Leu Gln Ser Gln Gly Asn Gly Ser Cys Ser Val Lys		
405	410	415
Arg His Glu Val Gln Phe Gly Val Asn Ala Ile Ser Gly Cys Lys Leu		
420	425	430
Arg Leu Lys Lys Ala Asp Cys Ser His Leu Gln Gln Glu Ile Tyr Gln		
435	440	445
Thr Leu His Gly Arg Pro Arg Pro Glu Tyr Val Ala Ile Phe Gly Asn		
450	455	460
Ala Asp Pro Ala Gln Lys Gly Gly Trp Thr Arg Ile Leu Asn Arg His		
465	470	475
Cys Ser Ile Ser Ala Ile Asn Cys Thr Ser Cys Cys Leu Ile Pro Val		
485	490	495
Ser Leu Glu Ile Gln Val Leu Trp Ala Tyr Val Gly Leu Leu Ser Asn		
500	505	510
Pro Gln Ala His Val Ser Gly Val Arg Phe Leu Tyr Gln Cys Gln Ser		
515	520	525
Ile Gln Asp Ser Gln Gln Val Thr Glu Val Ser Leu Thr Thr Leu Val		
530	535	540
Asn Phe Val Asp Ile Thr Gln Lys Pro Gln Pro Pro Arg Gly Gln Pro		
545	550	555
Lys Met Asp Trp Lys Trp Pro Phe Asp Phe Phe Pro Phe Lys Val Ala		
565	570	575
Phe Ser Arg Gly Val Phe Ser Gln Lys Cys Ser Val Ser Pro Ile Leu		
580	585	590
Ile Leu Cys Leu Leu Leu Leu Gly Val Leu Asn Leu Glu Thr Met Xaa		
595	600	605

<210> 69

<211> 90

<212> PRT

<213> Homo sapiens

<220>
 <221> SITE
 <222> (90)
 <223> Xaa equals stop translation

 <400> 69
 Met Ala Leu Arg Phe Leu Leu Leu Ser Ile Gly Pro Val Pro Ser Leu
 1 5 10 15
 Gly Asn Ile Ala Ala Ala Gly Ser Asp Glu Lys Cys Lys Leu Ala Met
 20 25 30
 Gln Arg Gly Ala Gln Ser Ser Val Asn Tyr Ser Gln Gly Ser Leu Lys
 35 40 45
 Asp Ala Ala Ser Ala Ser Thr Arg Thr Ala Ser Gly Trp Val Lys Arg
 50 55 60
 Asn Arg Ser Arg Glu Asn Gln Glu Met Leu Ile Tyr Ser Lys Asn Lys
 65 70 75 80
 Ile Pro Ile Trp Lys Ile Ser Lys Lys Xaa
 85 90

<210> 70
 <211> 117
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (117)
 <223> Xaa equals stop translation

 <400> 70
 Met Ala Gly Leu Ile Phe Val Leu His Ser Cys Phe Arg Phe Ile Thr
 1 5 10 15
 Phe Val Cys Pro Thr Ser Ser Asp Pro Leu Arg Thr Cys Ala Val Leu
 20 25 30
 Leu Cys Val Gly Tyr Gln Asp Leu Pro Asn Pro Val Phe Arg Tyr Leu
 35 40 45
 Gln Ser Val Asn Glu Leu Leu Ser Thr Leu Leu Asn Ser Asp Ser Pro
 50 55 60
 Gln Gln Val Leu Gln Phe Val Pro Met Glu Val Leu Leu Lys Gly Ala
 65 70 75 80
 Leu Leu Asp Phe Leu Trp Asp Leu Asn Ala Ala Ile Ala Lys Arg His
 85 90 95
 Leu His Phe Ile Ile Gln Arg Glu Arg Glu Glu Ile Ile Asn Ser Leu
 100 105 110

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Gln Leu Gln Asn Xaa
115

<210> 71
<211> 140
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (140)
<223> Xaa equals stop translation

<400> 71
Met Cys Val Trp Gly Val Cys Val Cys Val Val Ala Arg Val Cys Val
1 5 10 15
Trp Leu Gly Leu Ala Glu Leu Phe Arg Gly Arg Val Arg Asp Cys Gly
20 25 30
Lys Ile Thr His Phe Pro Thr Tyr Leu Leu Tyr Trp Thr Leu Lys Asn
35 40 45
Asn Asn Lys His Gln Val Lys Phe Leu Asn His Val Leu Cys Val Cys
50 55 60
Val Cys Val Cys Val Cys Val Cys Ile Cys Lys Cys Ile Cys Ile Cys
65 70 75 80
Met Leu Leu Tyr Phe Gln Val Asn Asn Tyr Ile Glu Asp Cys Ile Ala
85 90 95
Gln Lys His Ser Leu Ile Lys Val Leu Arg Leu Val Cys Leu Gln Ser
100 105 110
Val Cys Asn Ser Gly Leu Lys Gln Lys Val Leu Asp Tyr Tyr Lys Arg
115 120 125
Glu Ile Leu Gln Val Ser Ile Phe Leu Asn Tyr Xaa
130 135 140

<210> 72
<211> 96
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (96)
<223> Xaa equals stop translation

<400> 72
Met His Leu Cys Ile Cys Ala Val Trp Val Leu Val Ala Leu Leu Arg
1 5 10 15
Met His Gly Ala Ser Pro Ala Gln Thr Ser Gly Thr Arg Ser Gly Asn

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	20		25		30
Gly Gly Cys Arg Arg His Gly Ala Gly Gln Gly Arg Gly Ala Ala Thr					
35		40		45	
Gln Pro Leu Arg Pro Pro Arg Gly Thr Ala Ser Gly Gln Leu Met Ala					
50		55		60	
Leu Leu Ser Ala Leu Leu Pro Arg Leu Ser Gly Ser Ser Thr Pro Met					
65		70		75	80
Met Ala His Gly Arg Pro Ala Pro Pro Gln Trp Ser Arg Val Ser Xaa					
	85		90		95

<210> 73
 <211> 78
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (78)
 <223> Xaa equals stop translation

<400> 73
Met Ser Leu Tyr Lys Ile His Leu Leu Leu Tyr Val Ala Val Leu Ser
1 5 10 15
Ser Val Ala Ser Ser Tyr Pro Glu Ala Gln His Met Ser Pro Gly Gln
20 25 30
Val Pro Lys Phe Gln Ala Val Leu Ser Val Lys Ala Gly Val Cys Met
35 40 45
Cys Tyr Gln His Met Ile Arg Gly Arg Pro Thr Gln Gly Ala Val Ser
50 55 60
Val Ala Gln Gln Ser Thr Thr Phe Thr Val Ala Tyr Phe Xaa
65 70 75

<210> 74
 <211> 55
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (55)
 <223> Xaa equals stop translation

<400> 74
Met Ala Val Arg Leu Ile Lys Pro Ala Val Phe Ala Val Leu Ala Gly
1 5 10 15

Phe Ser Val Leu Trp Leu Ser Pro Ala Ser Leu Ala Ala Ser Phe Asp
 20 25 30

Cys Asp Arg Ala Lys Arg Leu Thr Arg Lys Pro Ser Val Pro Arg Ala
 35 40 45

Pro Ser Met Ile Arg Thr Xaa
 50 55

<210> 75
 <211> 210
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (181)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (200)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (207)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (210)
 <223> Xaa equals stop translation

<400> 75
 Met Tyr Phe Leu Phe Phe Phe Ala Phe Phe Phe Phe Pro Leu Phe Cys
 1 5 10 15

Tyr Cys Phe Asn Tyr Asn Lys Arg Ala Arg Gly Ser Gln Ala Leu Ala
 20 25 30

Arg Ser Trp Arg Pro Met Gly Val Leu Gly Arg Gly Arg Gly Glu Val
 35 40 45

Ser Gly Gly Gln Arg Trp Arg Val Lys Asn Glu Lys Val Gly Glu Leu
 50 55 60

Gly Leu Ala Gln Glu Pro Cys Val Pro Ala His Ser Pro Pro Ser Leu
 65 70 75 80

Pro Leu Pro Thr Ser Leu Pro Leu His Gly Phe Ser Pro Pro Leu Pro
 85 90 95

Glu Ser Tyr Gly Thr Gly Pro Cys Ser Ser Gly Ile Gln Leu Leu Pro
 100 105 110

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Ala His Ser Ser Ser Trp Ala Thr Ser Pro Pro Thr Phe Asp Val Ser
 115 120 125

Pro Pro Val Ala Thr Leu Gln Leu Ala Phe Gln Ala Pro Ser Arg Gly
 130 135 140

Arg Pro Leu Pro Arg Pro Leu Thr His Val Ala Ile Pro Thr Trp Leu
 145 150 155 160

Pro Val Met Ser Leu Leu Ser Lys Pro Ser Cys Pro Leu Phe Leu Pro
 165 170 175

Pro Arg His Ala Xaa Thr Lys Trp Trp Lys Pro Pro Leu Ser Pro Ser
 180 185 190

Leu Pro Cys Ala Glu Phe Ser Xaa Val Leu Asn Glu Gly Glu Xaa Asp
 195 200 205

Lys Xaa
 210

<210> 76
 <211> 105
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (89)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (105)
 <223> Xaa equals stop translation

<400> 76
 Met Pro Thr Ser Ser Tyr Arg Ser Val Trp Pro Leu Thr Leu Leu Ala
 1 5 10 15

Leu Lys Ser Thr Ala Cys Ala Leu Ala Phe Thr Arg Met Pro Gly Phe
 20 25 30

Gln Thr Pro Ser Glu Phe Leu Glu Asn Pro Ser Gln Ser Ser Arg Leu
 35 40 45

Thr Ala Pro Phe Arg Lys His Val Arg Pro Lys Lys Gln His Glu Ile
 50 55 60

Arg Arg Leu Gly Glu Leu Val Lys Lys Pro Ser Asp Phe Thr Gly Cys
 65 70 75 80

Thr Gln Val Val Asp Val Gly Ser Xaa Gln Gly His Leu Ser Arg Phe
 85 90 95

Met Ala Leu Gly Leu Gly Leu Met Xaa
 100 105

<210> 77
 <211> 176
 <212> PRT
 <213> Homo sapiens

<400> 77
 Met Leu Leu Leu Met Leu Val Asn Thr Ser Ala Val Ala Cys Thr His
 1 5 10 15
 Gly Gly Arg Gly Pro Trp Gly Asn Ser Ala Ala Gln Ala Cys Ala Ala
 20 25 30
 Leu Ala Pro Trp Pro Arg Gln Asp Pro Ser Ala Ala Ser Gln Trp Gln
 35 40 45
 Pro Gln Val Leu Val Gly Leu Leu Ser Tyr His Gly Trp Gly Gly Gln
 50 55 60
 Arg Leu Ser Pro Cys Pro Arg Ser Ile Cys Cys Val Ser Thr Arg His
 65 70 75 80
 Leu Glu Gly Ala Arg Ser Lys Ala Gln Gly Pro Ala Ala Trp Leu His
 85 90 95
 Met Glu Val Arg Val Pro Arg Val Gln Pro Pro Ala Leu Gln Val Pro
 100 105 110
 Ser Ser Ser Asp Lys Ala Gly Gln Gly Arg Trp Gly Val Pro Gly Gln
 115 120 125
 Arg Gly Leu Val Gly Arg Gly Gly Gly Cys Lys Val Thr Pro Ser Leu
 130 135 140
 Pro Cys Arg Arg Thr Glu Arg Lys Arg Thr Ala Ala Ser Ala Lys Val
 145 150 155 160
 Thr Cys Pro Ala Ser Ser Arg Arg Pro Trp Gly Trp Gln Ser Ser Pro
 165 170 175

<210> 78
 <211> 45
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (45)
 <223> Xaa equals stop translation

<400> 78
 Met His Lys Asn Asn Leu Phe Leu Cys Val Leu Phe Arg Leu Leu Phe
 1 5 10 15

Arg Cys Ser Cys Phe Asn Leu Leu Asn Phe Pro Gln Thr Tyr Ala Val
 20 25 30

Gly Lys Gly Gln Ala Gly Lys Asp Gln Cys Ser Ser Xaa
 35 40 45

<210> 79

<211> 71

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (71)

<223> Xaa equals stop translation

<400> 79

Met Asp Ser Val Thr Ala Gly Leu Phe Met Leu Ser Phe Leu Leu Tyr
 1 5 10 15

Leu Pro Ser Ser Ala Phe Ser Gly His Trp Tyr Pro Tyr Pro Gly Val
 20 25 30

Val Ser Trp Ser Asn Ser Cys Leu Ala Gly Leu Asn Cys Gly Val Ser
 35 40 45

Gly Pro Lys Ala Ile Gly Thr Ser Val Val Tyr Phe Leu Ile Pro Ile
 50 55 60

Leu Trp Arg Phe Val Phe Xaa
 65 70

<210> 80

<211> 56

<212> PRT

<213> Homo sapiens

<400> 80

Met Cys Leu Ala Phe Ser Val Ile Ile Leu Ala Gly Ala Gly Ser Ser
 1 5 10 15

Arg Ser Trp Asn Ser Val Leu Val Glu Lys Glu Val Val Glu Gly Gly
 20 25 30

Leu Gly Pro Trp Gly Asn Cys Ser Ala Glu Pro Leu Pro His Leu Leu
 35 40 45

Leu Pro Arg Thr Asn Leu Lys Gly
 50 55

<210> 81

<211> 49

<212> PRT

<213> Homo sapiens

<220>
 <221> SITE
 <222> (49)
 <223> Xaa equals stop translation

<400> 81

Met Cys His Phe Ser Ala Leu Ser Phe Thr Phe Cys Val Leu Pro Leu
 1 5 10 15

Ala Phe Ser Phe Leu Gln Lys His Cys Tyr Phe Thr His Lys Phe Gly
 20 25 30

Gln Asn Val Gln Tyr Ser His Phe Arg Val Ser Phe Gln Trp Lys Lys
 35 40 45

Xaa

<210> 82
 <211> 46
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (46)
 <223> Xaa equals stop translation

<400> 82

Met Leu Val Ser Leu Ile Ile Cys Leu Leu Leu Asp Leu Leu Asn Gln
 1 5 10 15

Pro Ser Leu Leu Arg Asp Leu Ile Leu Lys Gln His Thr Gly Asn Pro
 20 25 30

His Leu Ser Phe Pro Leu Lys Tyr Ser His Trp Met Gly Xaa
 35 40 45

<210> 83
 <211> 91
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (91)
 <223> Xaa equals stop translation

<400> 83

Met Ala Ile Arg Leu Val Phe Leu Ala Leu Ala Gly Leu Val Asp Gly
 1 5 10 15

Lys Pro Val Trp Ile Thr Leu Trp Met Asp Ala Lys Arg Pro Asn Leu
 20 25 30

Ala Gly Thr Gly Ser Thr Trp Gly Ser Arg Arg Asp Ser His Cys Cys
 35 40 45

His Gly Pro Thr Ala Trp Ser Leu Pro Cys Leu Leu Cys Leu Phe Arg
 50 55 60

Ala Gln Gln Lys Asp Arg Glu Arg Ser Leu Leu Gly Val Pro Leu Pro
 65 70 75 80

Thr Leu Gln Gly Gly Asn Leu Ser Asp Gly Xaa
 85 90

<210> 84

<211> 103

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (92)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (103)

<223> Xaa equals stop translation

<400> 84

Met Gly Arg Arg Ser Gly Leu Leu Gly Leu Arg Pro Gly Arg Ser Arg
 1 5 10 15

Trp Arg Trp Ser Gly Ser Val Trp Val Arg Ser Val Leu Leu Leu Leu
 20 25 30

Gly Gly Leu Arg Ala Ser Ala Thr Ser Thr Pro Val Ser Leu Gly Ser
 35 40 45

Ser Pro Pro Cys Arg His His Val Pro Ser Asp Thr Glu Val Ile Asn
 50 55 60

Lys Val His Leu Lys Ala Asn His Val Val Lys Arg Asp Val Asp Glu
 65 70 75 80

His Leu Arg Ile Lys Thr Val Tyr Asp Lys Xaa Xaa Xaa Ser Cys Ser
 85 90 95

Leu Arg Lys Arg Ile Leu Xaa

100

<210> 85
 <211> 45
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (45)
 <223> Xaa equals stop translation

<400> 85
 Met Gln Cys Asp Thr Phe Ser Lys Ala Thr Cys Cys Lys Ile Leu Leu
 1 5 10 15
 Leu Ser Cys Cys Val Leu Tyr Leu Val Phe Ser Arg Leu Arg Gly Leu
 20 25 30
 Asp Gln Arg Ser Lys Arg Tyr Ser Leu Pro Asp His Xaa
 35 40 45

<210> 86
 <211> 67
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (67)
 <223> Xaa equals stop translation

<400> 86
 Met Asn Tyr Ile Phe Leu Leu Met Ala Leu Pro His Leu Ile Ala Ile
 1 5 10 15
 Ala Leu Thr Trp Gly Arg Tyr Ser Phe Ser Cys Leu Ala Asn Lys Glu
 20 25 30
 Thr Glu Phe Gln Arg Cys Gln Val Thr Cys Leu Leu His Thr Leu Gly
 35 40 45
 Val Leu Met Phe Asn Phe Glu Leu Arg Ser Ile Trp Leu Glu Ser Ser
 50 55 60
 Leu His Xaa
 65

<210> 87
 <211> 72
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE

<222> (72)

<223> Xaa equals stop translation

<400> 87

Met Leu Phe Leu Asn Leu Thr Val Thr Cys Ile Phe Leu Phe Cys Phe
 1 5 10 15

Tyr Phe Asn Val Leu Val Ala His Leu Met Asn Val Asn Leu Lys Asn
 20 25 30

Ser Val Gln Leu Ser Arg Tyr Asn Ser Ala Lys Gln Ile Leu Lys Leu
 35 40 45

His Ile Thr Leu Gln His Met Val Pro His Thr Leu Ile Val Ala Phe
 50 55 60

Tyr Ile Phe Ser Tyr Tyr Tyr Xaa
 65 70

<210> 88

<211> 212

<212> PRT

<213> Homo sapiens

<400> 83

Met Lys Thr Leu Pro Ala Met Leu Gly Thr Gly Lys Leu Phe Trp Val
 1 5 10 15

Phe Phe Leu Ile Pro Tyr Leu Asp Ile Trp Asn Ile His Gly Lys Glu
 20 25 30

Ser Cys Asp Val Gln Leu Tyr Ile Lys Arg Gln Ser Glu His Ser Ile
 35 40 45

Leu Ala Gly Asp Pro Phe Glu Leu Glu Cys Pro Val Lys Tyr Cys Ala
 50 55 60

Asn Arg Pro His Val Thr Trp Cys Lys Leu Asn Gly Thr Thr Cys Val
 65 70 75 80

Lys Leu Glu Asp Arg Gln Thr Ser Trp Lys Glu Glu Lys Asn Ile Ser
 85 90 95

Phe Phe Ile Leu His Phe Glu Pro Val Leu Pro Asn Asp Asn Gly Ser
 100 105 110

Tyr Arg Cys Ser Ala Asn Phe Gln Ser Asn Leu Ile Glu Ser His Ser
 115 120 125

Thr Thr Leu Tyr Val Thr Gly Glu Phe Ser Thr Pro Arg Pro Ser Asp
 130 135 140

Ile Phe Leu Ile Met Phe Pro Gly Arg Gly Gly Phe Ser Phe Ser Ser
 145 150 155 160

Asp Tyr Val Arg Lys Pro Thr Pro Ile Ala His Leu Lys Ser Ala Thr
 165 170 175

Pro His Arg Leu Leu Cys Ala Ser Val Tyr Ile Cys Val Cys Met Cys
 180 185 190
 Ala Phe Glu Val Ser Glu Ile Glu Glu Ser Arg Glu Ile Asp Ser Lys
 195 200 205
 Ser Tyr Cys Phe
 210

<210> 89
 <211> 111
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (111)
 <223> Xaa equals stop translation

<400> 89
 Met Thr Val Ser Tyr Phe Trp Trp Leu Arg Val Gly Ala Trp Ala Glu
 1 5 10 15
 Asp Val Glu Ala Leu Ala Ser Leu Pro Glu Asp Arg Leu Arg Trp Asn
 20 25 30
 Leu Leu Ala Leu Pro Ala Ser Pro Cys Ala Val Thr Ala Leu Val Ala
 35 40 45
 Arg His Arg Arg Ala Gly Leu Gln Arg Ser Ile Gln Cys Leu Leu Gly
 50 55 60
 Arg Gln Gly Gly Gly Gly Cys Asn Cys Glu Leu Thr Lys Pro Gln Val
 65 70 75 80
 Gly Ser Lys Trp Val Gly His Arg Lys Lys Ser Asp Leu Gln Ser Gly
 85 90 95
 Asp Leu Gly Ser Gly Leu Cys Leu Met Thr Gly Ser Val Met Xaa
 100 105 110

<210> 90
 <211> 42
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (42)
 <223> Xaa equals stop translation

<400> 90
 Met Val Lys Val Gly Ala Trp Arg Ala Val Gln Ile Leu Met Leu Phe
 1 5 10 15

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Ala Asn Pro Gly His Ala Glu Gly Ala Cys Ile Ser Pro Gly Pro Ala
20 25 30

Gly Lys Arg Glu Pro Leu Lys Leu Gly Xaa
35 40

<210> 91

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (59)

<223> Xaa equals stop translation

<400> 91

Met Val Ala Thr Leu Cys Leu Glu Asn Ser Ser Val Ser Leu Trp Phe
1 5 10 15

Ile Phe Leu Ser Ser Leu Ser Ser Phe Pro Trp Cys Gly Ala Leu Ser
20 25 30

Asp Asn Trp Pro Ser Gly Gly Ala Val Ala Arg Cys His Ser Gly Arg
35 40 45

Arg Trp Phe Pro Glu Gly Ser Xaa Cys Leu Xaa
50 55

<210> 92

<211> 77

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals stop translation

<400> 92

Met Phe Cys Ile Gln Gln Lys Trp Leu Phe Ser Phe Leu Phe Tyr Glu
1 5 10 15

Val Gly Leu Met Gly Ile Asp Ser Leu Arg Lys Lys Tyr Asn Cys Lys
20 25 30

Ser Val Glu Val Phe Pro Ser Gln Asp Val Lys Cys Gln Arg Ser Asp
35 40 45

Ser Cys Gly Arg Met Gly Ser Lys Leu Tyr Lys Ser Leu Glu Met Asn
50 55 60

Glu Val Arg Gln Leu Ser Leu Arg Gln Lys Thr Met Xaa
 65 70 75

<210> 93
 <211> 69
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (69)
 <223> Xaa equals stop translation

<400> 93
 Met Ala Lys Leu Met Tyr Tyr Gln Ile Leu Cys Leu Val Val Phe Cys
 1 5 10 15

Trp Leu Ile His Ser Phe Ile His Leu Phe Asn Lys His Phe Leu Ile
 20 25 30

Ala Phe Tyr Val Pro Gly Pro Ala Ile Asp Ala Arg Asp Ser Ala Val
 35 40 45

Ser Thr Thr Asp Lys Glu Phe Cys His Cys Gly Val Tyr Ile Leu Val
 50 55 60

Ala Gly Asp Arg Xaa
 65

<210> 94
 <211> 44
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (44)
 <223> Xaa equals stop translation

<400> 94
 Met Glu Thr Thr Gly Ser Trp Thr Cys Leu Phe Asn Leu Val Ala Ile
 1 5 10 15

Ile Ser Asn Leu Gly Leu Cys Thr Phe Leu Val Phe Gly Gln Ala Gln
 20 25 30

Arg Val Asp Leu Ser Ser Thr His Glu Asp Leu Xaa
 35 40

<210> 95
 <211> 47
 <212> PRT
 <213> Homo sapiens

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<220>
<221> SITE
<222> (47)
<223> Xaa equals stop translation

<400> 95
Met Lys Ala Gln Met Leu Leu Ser Leu Ala Trp Pro Leu Pro Leu Ser
1 5 10 15
Thr Ala Asn Ser Cys Leu Pro Gln Phe Pro Arg Gly Leu Tyr Ser Ala
20 25 30
His Tyr Cys Pro Ser Cys Leu Leu Phe Leu Glu Ala Leu Ser Xaa
35 40 45

<210> 96
<211> 48
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (48)
<223> Xaa equals stop translation

<400> 96
Met Cys Leu Leu Ser Phe Asn Cys Lys Ala Val Leu Ser Leu Ser Leu
1 5 10 15
Ile Ser Leu Ser Phe Leu Cys Cys Leu Glu Leu Cys Leu Ala Arg Cys
20 25 30
Gly Gly Arg Arg Asn Val Ser Ala Pro Leu Lys Met Phe Ile Ile Xaa
35 40 45

<210> 97
<211> 154
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (154)
<223> Xaa equals stop translation

<400> 97
Met Leu Val Thr Ala Tyr Leu Ala Phe Val Gly Leu Leu Ala Ser Cys
1 5 10 15
Leu Gly Leu Glu Leu Ser Arg Cys Arg Ala Lys Pro Pro Gly Arg Ala
20 25 30
Cys Ser Asn Pro Ser Phe Leu Arg Phe Gln Leu Asp Phe Tyr Gln Val

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35 40 45
 Tyr Phe Leu Ala Leu Ala Ala Asp Trp Leu Gln Ala Pro Tyr Leu Tyr
 50 55 60
 Lys Leu Tyr Gln His Tyr Tyr Phe Leu Glu Gly Gln Ile Ala Ile Leu
 65 70 75 80
 Tyr Val Cys Gly Leu Ala Ser Thr Val Leu Phe Gly Leu Val Ala Ser
 85 90 95
 Ser Leu Val Asp Trp Leu Gly Arg Lys Asn Ser Cys Val Leu Phe Ser
 100 105 110
 Leu Thr Tyr Ser Leu Cys Cys Leu Thr Lys Leu Ser Gln Asp Tyr Phe
 115 120 125
 Val Leu Leu Val Gly Arg Ala Leu Gly Gly Leu Ser Thr Ala Ala Leu
 130 135 140
 Leu Ser Leu Arg Gly Leu Val Tyr Pro Xaa
 145 150

<210> 98
 <211> 46
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (46)
 <223> Xaa equals stop translation

<400> 98
 Met Gln Ala His Pro Ile Phe Ile Tyr His Lys Arg Val Phe Phe Leu
 1 5 10 15
 Leu Lys Phe Ile Phe Tyr Ile Ile Phe Cys Phe Phe Phe Leu Asp Ile
 20 25 30
 Ser Thr Leu Tyr Cys Ser Leu Ser Thr Phe Cys Lys Lys Xaa
 35 40 45

<210> 99
 <211> 48
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (48)
 <223> Xaa equals stop translation

<400> 99
 Met Gly Val Leu Leu Leu Phe Ser Phe Phe Phe Pro Asn Gly Ser Phe
 1 5 10 15

Ser Pro Val Val Leu Pro Ser Tyr Phe Pro Asn Ser Ser Ser Tyr Phe
 20 25 30

Val Phe Cys Thr Ser Phe Trp Arg Pro Leu Ser Phe Gln Lys Gly Xaa
 35 40 45

<210> 100

<211> 51

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> Xaa equals stop translation

<400> 100

Met Arg Arg Cys Phe Leu Val Leu Glu Ile Ser Val Cys Leu Met Val
 1 5 10 15

Ile Ile Val Phe Leu Asp Phe Trp Val Gly Gly Pro Gly Arg Gly Arg
 20 25 30

Leu Arg Asn Lys Ser Val Pro Gln Ile Thr Ser Ile Trp Lys Glu Phe
 35 40 45

Phe Val Xaa
 50

<210> 101

<211> 41

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals stop translation

<400> 101

Met Cys Phe Arg Phe Met Met Ile Ile Phe Leu Thr Asn Val Ile Ser
 1 5 10 15

Val Ser Ala Val Ile Phe Lys Leu Arg Glu Arg Asp Ser Ile Arg Phe
 20 25 30

Phe Phe Phe Phe Ile Phe Leu Lys Xaa
 35 40

<210> 102

<211> 50

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<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (50)

<223> Xaa equals stop translation

<400> 102

Met Gly Phe Ser Ile Ile Phe Arg Pro Glu Ala Ala Arg Pro Glu Val
1 5 10 15

Arg Leu His Leu Ser Ala Leu Phe Val Leu Leu Leu Ala Thr Leu Gly
20 25 30

Phe Leu Leu Gly Thr Met Cys Gly Cys Gly Met Cys Glu Gln Lys Gly
35 40 45

Gly Xaa
50

<210> 103

<211> 75

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals stop translation

<400> 103

Met Thr Leu Leu Leu Phe Ile Phe Phe Val Asp Cys Phe Ser Thr Pro
1 5 10 15

Gly Ser Ser Val Phe Asp Thr Gln Glu Val Trp Val Val Val Tyr Ser
20 25 30

Val Asn Lys Leu Leu Ala Val Gln His Cys Gln Gly Ile Ala Pro Asn
35 40 45

Val Tyr Ala Leu Ala Val Lys Lys Ser Val Cys Asn Val Ser Glu Trp
50 55 60

Ser Leu Val Ile Cys His Pro Met Pro Ile Xaa
65 70 75

<210> 104

<211> 43

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (43)

<223> Xaa equals stop translation

<400> 104

Met Ile Phe Leu Leu Phe Leu Thr Pro Leu Trp Leu Gln Lys Gly Ser
 1 5 10 15

Ala Gly Lys Met Ser Gly Glu Phe Leu Tyr Ala Ser Leu Phe Gln Trp
 20 25 30

Asn Tyr Phe Trp Arg Asn Lys Lys Val Cys Xaa
 35 40

<210> 105

<211> 123

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (123)

<223> Xaa equals stop translation

<400> 105

Met Leu Met Leu Ala Val Leu Met Ala Ala Thr His Ala Val Tyr Gly
 1 5 10 15

Lys Leu Leu Leu Phe Glu Tyr Arg His Arg Lys Met Lys Pro Val Gln
 20 25 30

Met Val Pro Ala Ile Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala
 35 40 45

Thr Gly Gln Ala Ala Ala Asn Trp Ile Ala Gly Phe Gly Arg Gly Pro
 50 55 60

Cys His Gln Pro Cys Trp Val Ser Gly Arg Met Gly Met Gln Pro Ala
 65 70 75 80

Gly Gly Tyr Trp Ala Trp Thr Arg Ser Arg Val Lys Ser Ser Trp Ala
 85 90 95

Ala Cys Ser Thr Arg Ser His Cys Ser Phe Cys Ser Ser Gly His Pro
 100 105 110

Thr Ser Trp Pro Ala Thr Gly Glu Cys Leu Xaa
 115 120

<210> 106

<211> 56

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (56)

<223> Xaa equals stop translation

<400> 106

Met Leu Leu Leu Met Leu Val Asn Thr Ser Ala Val Ala Cys Thr His
 1 5 10 15

Gly Gly Arg Gly Pro Trp Gly Asn Ser Ala Ala Gln Ala Cys Ala Ala
 20 25 30

Leu Ala Arg Gly Pro Gly Arg Thr Leu Pro Arg Pro Pro Ser Gly Ser
 35 40 45

His Arg Cys Trp Leu Val Cys Xaa
 50 55

<210> 107

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (61)

<223> Xaa equals stop translation

<400> 107

Met Xaa Leu Ala Phe Ser Val Ile Ile Leu Ala Gly Ala Gly Ser Ser
 1 5 10 15

Arg Ser Trp Asn Ser Val Leu Val Glu Lys Glu Val Val Glu Gly Gly
 20 25 30

Leu Gly Pro Trp Gly Asn Cys Ser Ala Glu Pro Leu Pro His Leu Leu
 35 40 45

Leu Pro Arg Thr Asn Leu Lys Ala Lys Val Pro Gly Xaa
 50 55 60

<210> 108

<211> 102

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (101)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (102)

<223> Xaa equals stop translation

<400> 108

Met Lys Thr Leu Pro Ala Met Leu Gly Thr Gly Lys Leu Phe Trp Val
 1 5 10 15

Phe Phe Leu Ile Pro Tyr Leu Asp Ile Trp Asn Ile His Gly Lys Glu
 20 25 30

Ser Cys Asp Val Gln Leu Tyr Ile Lys Arg Gln Ser Glu His Ser Ile
 35 40 45

Leu Ala Gly Asp Pro Phe Glu Leu Glu Cys Pro Val Lys Tyr Cys Ala
 50 55 60

Asn Arg Pro His Val Thr Trp Cys Lys Leu Asn Gly Thr Thr Cys Val
 65 70 75 80

Lys Leu Glu Asp Arg Gln Thr Ser Trp Lys Lys Arg Arg Thr Phe His
 85 90 95

Phe Ser Ser Thr Xaa Xaa
 100

<210> 109

<211> 55

<212> PRT

<213> Homo sapiens

<400> 109

Val Lys Val Lys Glu Lys Ser Ala Ala Glu Gly Thr Gly Lys Lys Pro
 1 5 10 15

Lys Gly Cys Arg Leu Pro Gly Val Leu Gly Glu Pro Pro Ser Ser Ala
 20 25 30

Gly Pro Arg Lys Gln Arg Arg Thr Val Glu Lys Gly Gly Gly Gln Gly
 35 40 45

Gly Asn Ser Arg Ala Ala Ser
 50 55

<210> 110

<211> 14

<212> PRT

<213> Homo sapiens

<400> 110

Glu Glu His Arg Tyr Phe Lys Ala Asn Asp Thr Leu Gly Phe
 1 5 10

<210> 111

<211> 14

<212> PRT

<213> Homo sapiens

<400> 111

Gly Thr Ser Gly Thr Ser Gly Thr Arg Trp Asn Val His Phe
 1 5 10

<210> 112

<211> 77

<212> PRT

<213> Homo sapiens

<400> 112

Asp Gly Ala Gly Ala Phe Arg Ala Pro Ile Arg Glu Pro Gly Val Pro
 1 5 10 15

Ala Ser Pro Gln Pro Pro Glu Pro Gly Gln Leu Leu Arg Arg Arg Gln
 20 25 30

Gly His Arg Gly Gly Val Gly Ser Pro Arg Thr Pro Ala Gly Gly Ser
 35 40 45

Arg Gly Arg Arg Leu Pro Ala Thr Lys Arg Gly Thr Ser Gly Arg Arg
 50 55 60

Ala Arg Gly Ser Ser Gly Arg Ile Asn Ala Ser Gln Thr
 65 70 75

<210> 113

<211> 217

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (55)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (57)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (58)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (131)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (158)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (175)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 113

Gln His Gly Leu Gln Ile Leu Leu Gln Arg Asp Gly Val Pro Gly Gly
 1 5 10 15

Asp Ala Gly Glu Pro His Gly Gln Xaa Arg Gly Leu His Ala Gln Gln
 20 25 30

Leu His Arg Pro Val Gly Ser Val Asp Leu Trp Ile Phe Arg Val Asp
 35 40 45

Ala Ala Gly Ser Gly Pro Xaa Val Xaa Xaa Gly Asn Glu Leu Arg His
 50 55 60

Leu Gln Gly Leu Pro Gly Thr Val Gly His Pro Arg Thr Met Asp Glu
 65 70 75 80

Thr Gly Pro Pro Ala Val Gly Glu Pro Arg Ser Gly Pro Ser Ala Gly
 85 90 95

Ser Ala Gly Pro Thr Ala Ala Ala Ser Pro Arg Pro Ala Ala Thr Ser
 100 105 110

Pro Thr Gly Arg Ala His Ile Ala Gly Arg Cys Ser Gln Pro Thr Ala
 115 120 125

Asp Asp Xaa Pro Glu Phe Val Cys Leu Lys Thr Leu Leu Leu Cys Leu
 130 135 140

Arg Met Gly Glu Met Arg Ser Glu Ala Pro Gly Ala Ala Xaa Glu Lys
 145 150 155 160

Asn Asn Phe Tyr Arg Asp Ala Arg Asp Ser Arg Gly Ser Gly Xaa Gly
 165 170 175

Thr Gly Gly Asn Ala Ala Cys Ala Gln Ser Pro Leu Pro Arg Thr Ser
 180 185 190

Lys Ile Arg Ser Lys Leu Arg Gly Arg Gly Trp Gly Cys Arg Gly Gly
 195 200 205

Asp Ser Glu Pro Pro Val Arg Lys Gln
 210 215

<210> 114

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 114

Gln His Gly Leu Gln Ile Leu Leu Gln Arg Asp Gly Val Pro Gly Gly
 1 5 10 15

Asp Ala Gly Glu Pro His Gly Gln Xaa Arg Gly Leu His Ala Gln Gln
 20 25 30

Leu His Arg Pro Val Gly Ser Val Asp Leu Trp Ile Phe Arg Val Asp
 35 40 45

Ala

<210> 115

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 115

Ala Gly Ser Gly Pro Xaa Val Xaa Xaa Gly Asn Glu Leu Arg His Leu
 1 5 10 15

Gln Gly Leu Pro Gly Thr Val Gly His Pro Arg Thr Met Asp Glu Thr
 20 25 30

Gly Pro Pro Ala Val Gly Glu Pro Arg Ser Gly Pro Ser Ala Gly Ser
 35 40 45

<210> 116

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 116

Ala Gly Pro Thr Ala Ala Ala Ser Pro Arg Pro Ala Ala Thr Ser Pro
 1 5 10 15

Thr Gly Arg Ala His Ile Ala Gly Arg Cys Ser Gln Pro Thr Ala Asp
 20 25 30

Asp Xaa Pro Glu Phe Val Cys Leu Lys Thr Leu Leu Leu Cys Leu Arg
 35 40 45

<210> 117

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (13)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (30)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 117

Met Gly Glu Met Arg Ser Glu Ala Pro Gly Ala Ala Xaa Glu Lys Asn
 1 5 10 15

Asn Phe Tyr Arg Asp Ala Arg Asp Ser Arg Gly Ser Gly Xaa Gly Thr
 20 25 30

Gly Gly Asn Ala Ala Cys Ala Gln Ser Pro Leu Pro Arg Thr Ser Lys
 35 40 45

<210> 118

<211> 24

<212> PRT

<213> Homo sapiens

<400> 118

Ile Arg Ser Lys Leu Arg Gly Arg Gly Trp Gly Cys Arg Gly Gly Asp
 1 5 10 15

Ser Glu Pro Pro Val Arg Lys Gln
 20

<210> 119
 <211> 16
 <212> PRT
 <213> Homo sapiens

<400> 119
 Gly Thr Ser Pro Glu Ala Tyr Val Gly Pro Gly Gly Pro Glu Cys Pro
 1 5 10 15

<210> 120
 <211> 20
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (11)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 120
 Ser Cys Ile His Thr Gly Asp Val Met Ile Xaa Pro Val Leu Ser Cys
 1 5 10 15

Phe Thr Arg Phe
 20

<210> 121
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 121
 Gly Arg His Leu Val Ala Ser Gln Lys Arg Val Leu Arg Asp Arg Arg
 1 5 10 15

Val Gln Thr Gly Ile Trp Ser Asp Gln Leu Tyr Ser Gln Arg Pro Trp
 20 25 30

Ala Pro Val Thr Trp Pro Asp His Trp Gly Val Cys Val Cys Val Tyr
 35 40 45

Val Cys
 50

<210> 122
 <211> 43
 <212> PRT
 <213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 122

Ala Phe Pro His Ser Ile Pro Cys Gln Val Met Ala Val Pro Ser Pro
 1 5 10 15

Gln Leu Leu Leu Glu Arg Pro Xaa Leu Pro Val Ser Phe Met Phe Leu
 20 25 30

Thr Ser His Pro Pro Pro Arg Leu Val Cys Pro
 35 40

<210> 123

<211> 361

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 123

Leu Pro Thr Leu His Ser Leu Ser Ser Tyr Gly Cys Pro Leu Thr Pro
 1 5 10 15

Ala Ala Pro Arg Glu Ala Leu Xaa Thr Cys Val Ile His Val Ser Asn
 20 25 30

Lys Pro Pro Ser Thr Pro Ser Cys Val Pro His Ala Pro Val His Leu
 35 40 45

Cys Cys Val Gly Val Gly Gly Pro Phe Ala His Ala Trp Gly Ile Pro
 50 55 60

Cys Pro Asp Gln Arg Asp Lys Glu Arg Glu Arg Arg Leu Gln Glu Ala
 65 70 75 80

Arg Gly Arg Pro Gly Glu Gly Arg Gly Asn Thr Ala Thr Glu Thr Thr
 85 90 95

Thr Arg His Ser Gln Arg Ala Ala Asp Gly Ser Ala Val Ser Thr Val
 100 105 110

Thr Lys Thr Glu Arg Leu Val His Ser Asn Asp Gly Thr Arg Thr Ala
 115 120 125

Arg Thr Thr Thr Val Glu Ser Ser Phe Val Arg Arg Ser Glu Asn Gly
 130 135 140

Ser Gly Ser Thr Met Met Gln Thr Lys Thr Phe Ser Ser Ser Ser
 145 150 155 160

Ser Lys Lys Met Gly Ser Ile Phe Asp Arg Glu Asp Gln Ala Ser Pro
 165 170 175

Arg Ala Gly Ser Leu Ala Ala Leu Glu Lys Arg Gln Ala Glu Lys Lys
 180 185 190
 Lys Glu Leu Met Lys Ala Gln Ser Leu Pro Lys Thr Ser Ala Ser Gln
 195 200 205
 Ala Arg Lys Ala Met Ile Glu Lys Leu Glu Lys Glu Gly Ala Ala Gly
 210 215 220
 Ser Pro Gly Gly Pro Arg Ala Ala Val Gln Arg Ser Thr Ser Phe Gly
 225 230 235 240
 Val Pro Asn Ala Asn Ser Ile Lys Gln Met Leu Leu Asp Trp Cys Arg
 245 250 255
 Ala Lys Thr Arg Gly Tyr Glu His Val Asp Ile Gln Asn Phe Ser Ser
 260 265 270
 Ser Trp Ser Asp Gly Met Ala Phe Cys Ala Leu Val His Asn Phe Phe
 275 280 285
 Pro Glu Ala Phe Asp Tyr Gly Gln Leu Ser Pro Gln Asn Arg Arg Gln
 290 295 300
 Asn Phe Glu Val Ala Phe Ser Ser Ala Glu Thr His Ala Asp Cys Pro
 305 310 315 320
 Gln Leu Leu Asp Thr Glu Asp Met Val Arg Leu Arg Glu Pro Asp Trp
 325 330 335
 Lys Cys Val Tyr Thr Tyr Ile Gln Glu Phe Tyr Arg Cys Leu Val Gln
 340 345 350
 Lys Gly Leu Val Lys Thr Lys Lys Ser
 355 360

<210> 124

<211> 46

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 124

Leu Pro Thr Leu His Ser Leu Ser Ser Tyr Gly Cys Pro Leu Thr Pro
 1 5 10 15
 Ala Ala Pro Arg Glu Ala Leu Xaa Thr Cys Val Ile His Val Ser Asn
 20 25 30
 Lys Pro Pro Ser Thr Pro Ser Cys Val Pro His Ala Pro Val
 35 40 45

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<210> 125
<211> 46
<212> PRT
<213> Homo sapiens

<400> 125
His Leu Cys Cys Val Gly Val Gly Gly Pro Phe Ala His Ala Trp Gly
1 5 10 15
Ile Pro Cys Pro Asp Gln Arg Asp Lys Glu Arg Glu Arg Arg Leu Gln
20 25 30
Glu Ala Arg Gly Arg Pro Gly Glu Gly Arg Gly Asn Thr Ala
35 40 45

<210> 126
<211> 46
<212> PRT
<213> Homo sapiens

<400> 126
Thr Glu Thr Thr Thr Arg His Ser Gln Arg Ala Ala Asp Gly Ser Ala
1 5 10 15
Val Ser Thr Val Thr Lys Thr Glu Arg Leu Val His Ser Asn Asp Gly
20 25 30
Thr Arg Thr Ala Arg Thr Thr Thr Val Glu Ser Ser Phe Val
35 40 45

<210> 127
<211> 46
<212> PRT
<213> Homo sapiens

<400> 127
Arg Arg Ser Glu Asn Gly Ser Gly Ser Thr Met Met Gln Thr Lys Thr
1 5 10 15
Phe Ser Ser Ser Ser Ser Ser Lys Lys Met Gly Ser Ile Phe Asp Arg
20 25 30
Glu Asp Gln Ala Ser Pro Arg Ala Gly Ser Leu Ala Ala Leu
35 40 45

<210> 128
<211> 47
<212> PRT
<213> Homo sapiens

<400> 128
Glu Lys Arg Gln Ala Glu Lys Lys Lys Glu Leu Met Lys Ala Gln Ser
1 5 10 15

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Leu Pro Lys Thr Ser Ala Ser Gln Ala Arg Lys Ala Met Ile Glu Lys
20 25 30

Leu Glu Lys Glu Gly Ala Ala Gly Ser Pro Gly Gly Pro Arg Ala
35 40 45

<210> 129

<211> 47

<212> PRT

<213> Homo sapiens

<400> 129

Ala Val Gln Arg Ser Thr Ser Phe Gly Val Pro Asn Ala Asn Ser Ile
1 5 10 15

Lys Gln Met Leu Leu Asp Trp Cys Arg Ala Lys Thr Arg Gly Tyr Glu
20 25 30

His Val Asp Ile Gln Asn Phe Ser Ser Ser Trp Ser Asp Gly Met
35 40 45

<210> 130

<211> 49

<212> PRT

<213> Homo sapiens

<400> 130

Ala Phe Cys Ala Leu Val His Asn Phe Phe Pro Glu Ala Phe Asp Tyr
1 5 10 15

Gly Gln Leu Ser Pro Gln Asn Arg Arg Gln Asn Phe Glu Val Ala Phe
20 25 30

Ser Ser Ala Glu Thr His Ala Asp Cys Pro Gln Leu Leu Asp Thr Glu
35 40 45

Asp

<210> 131

<211> 34

<212> PRT

<213> Homo sapiens

<400> 131

Met Val Arg Leu Arg Glu Pro Asp Trp Lys Cys Val Tyr Thr Tyr Ile
1 5 10 15

Gln Glu Phe Tyr Arg Cys Leu Val Gln Lys Gly Leu Val Lys Thr Lys
20 25 30

Lys Ser

<210> 132
 <211> 341
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (21)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (33)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (35)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (162)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (326)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (333)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 132
 Lys Met Glu Trp Leu Ala Asp Pro Thr Ala Trp Leu Gly Leu Leu Thr
 1 5 10 15
 Leu Ile Val Leu Xaa Leu Val Leu Gly Ile Asp Asn Leu Val Phe Ile
 20 25 30
 Xaa Ile Xaa Ala Xaa Lys Leu Pro Pro Glu Gln Arg Asp Arg Ala Arg
 35 40 45
 Leu Ile Gly Leu Ser Leu Ala Leu Leu Met Arg Leu Gly Leu Leu Ala
 50 55 60
 Ser Ile Ser Trp Leu Val Thr Leu Thr Gln Pro Leu Phe Glu Val Phe
 65 70 75 80
 Asp Lys Ser Phe Ser Gly Arg Asp Leu Ile Met Leu Phe Gly Gly Val
 85 90 95

Phe Leu Leu Phe Lys Ala Thr Met Glu Leu His Glu Arg Leu Glu Gly
 100 105 110
 His Val Ala Gln Arg Thr Gly Asn Val Ala Tyr Ala Met Phe Trp Pro
 115 120 125
 Ile Val Ala Gln Ile Val Val Leu Asp Ala Val Phe Ser Leu Asp Ala
 130 135 140
 Val Ile Thr Ala Val Gly Met Val Asp Glu Leu Ala Val Met Met Ile
 145 150 155 160
 Ala Xaa Ile Ile Ser Ile Gly Leu Met Ile Val Ala Ser Lys Pro Leu
 165 170 175
 Thr Arg Phe Val Asn Ala His Pro Thr Val Ile Met Leu Cys Leu Gly
 180 185 190
 Phe Leu Met Met Ile Gly Phe Ala Leu Thr Ala Glu Gly Leu Gly Phe
 195 200 205
 His Ile Pro Lys Gly Tyr Leu Tyr Ala Ala Ile Gly Phe Ser Ile Leu
 210 215 220
 Ile Glu Leu Phe Asn Gln Ile Ala Arg Ser Arg Arg Lys Lys Ser Ala
 225 230 235 240
 Gln Gly Thr Leu Pro Arg Arg Glu Arg Thr Ala His Ala Val Met Arg
 245 250 255
 Leu Leu Gly Gly Arg Asn Leu Ala Val Glu Glu Val Gly Glu Glu Val
 260 265 270
 Ala Asp Leu Leu Asp Asn Pro Asp Ala Asn Gly Gly Pro Leu Phe Asp
 275 280 285
 Arg Arg Glu Arg Val Met Ile Ser Gly Val Leu Gln Leu Ala Glu Arg
 290 295 300
 Pro Ile Arg Thr Leu Met Thr Pro Arg Ala Lys Val Asp Ser Ile Asp
 305 310 315 320
 Leu Ser Asp Asp Pro Xaa Thr Ile Arg Leu Lys Leu Xaa Ile Arg Leu
 325 330 335
 Thr Arg Ala Cys Pro
 340

<210> 133

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (21)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 133

Lys Met Glu Trp Leu Ala Asp Pro Thr Ala Trp Leu Gly Leu Leu Thr
1 5 10 15

Leu Ile Val Leu Xaa Leu Val Leu Gly Ile Asp Asn Leu Val Phe Ile
20 25 30

Xaa Ile Xaa Ala Xaa Lys Leu Pro Pro Glu Gln Arg Asp Arg Ala Arg
35 40 45

<210> 134

<211> 49

<212> PRT

<213> Homo sapiens

<400> 134

Leu Ile Gly Leu Ser Leu Ala Leu Leu Met Arg Leu Gly Leu Leu Ala
1 5 10 15

Ser Ile Ser Trp Leu Val Thr Leu Thr Gln Pro Leu Phe Glu Val Phe
20 25 30

Asp Lys Ser Phe Ser Gly Arg Asp Leu Ile Met Leu Phe Gly Gly Val
35 40 45

Phe

<210> 135

<211> 47

<212> PRT

<213> Homo sapiens

<400> 135

Leu Leu Phe Lys Ala Thr Met Glu Leu His Glu Arg Leu Glu Gly His
1 5 10 15

Val Ala Gln Arg Thr Gly Asn Val Ala Tyr Ala Met Phe Trp Pro Ile
 20 25 30

Val Ala Gln Ile Val Val Leu Asp Ala Val Phe Ser Leu Asp Ala
 35 40 45

<210> 136

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 136

Val Ile Thr Ala Val Gly Met Val Asp Glu Leu Ala Val Met Met Ile
 1 5 10 15

Ala Xaa Ile Ile Ser Ile Gly Leu Met Ile Val Ala Ser Lys Pro Leu
 20 25 30

Thr Arg Phe Val Asn Ala His Pro Thr Val Ile Met Leu Cys Leu Gly
 35 40 45

Phe

<210> 137

<211> 50

<212> PRT

<213> Homo sapiens

<400> 137

Leu Met Met Ile Gly Phe Ala Leu Thr Ala Glu Gly Leu Gly Phe His
 1 5 10 15

Ile Pro Lys Gly Tyr Leu Tyr Ala Ala Ile Gly Phe Ser Ile Leu Ile
 20 25 30

Glu Leu Phe Asn Gln Ile Ala Arg Ser Arg Arg Lys Lys Ser Ala Gln
 35 40 45

Gly Thr
 50

<210> 138

<211> 48

<212> PRT

<213> Homo sapiens

<400> 138

Leu Pro Arg Arg Glu Arg Thr Ala His Ala Val Met Arg Leu Leu Gly

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1 5 10

<210> 142
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 142
 His Lys Gly Ser Gly Arg Pro Pro Thr Lys Glu Ala Met Glu Pro Met
 1 5 10 15
 Glu Leu Met Glu Glu Met Leu Gly Leu Trp Val Ser Ala Asp Thr Pro
 20 25 30

<210> 143
 <211> 10
 <212> PRT
 <213> Homo sapiens

<400> 143
 Thr Val Lys His Glu Val Ile His Ala Leu
 1 5 10

<210> 144
 <211> 562
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (2)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (18)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (221)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (414)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 144

Glu Xaa Leu Leu Pro Glu Lys Lys Asn Leu Val Lys Asn Lys Leu Leu
 1 5 10 15
 Xaa Xaa Ala Ile Ser Tyr Leu Glu Lys Thr Phe Gln Val Arg Arg Pro
 20 25 30
 Ala Gly Thr Ile Leu Leu Ser Arg Gln Cys Ala Thr Asn Gln Tyr Leu
 35 40 45
 Arg Lys Glu Asn Asp Pro His Arg Tyr Cys Thr Gly Glu Cys Ala Ala
 50 55 60
 His Thr Lys Cys Gly Pro Val Ile Val Pro Glu Glu His Leu Gln Gln
 65 70 75 80
 Cys Arg Val Tyr Arg Gly Gly Lys Trp Pro His Gly Ala Val Gly Val
 85 90 95
 Pro Asp Gln Glu Gly Ile Ser Asp Ala Asp Phe Val Leu Tyr Val Gly
 100 105 110
 Ala Leu Ala Thr Glu Arg Cys Ser His Glu Asn Ile Ile Ser Tyr Ala
 115 120 125
 Ala Tyr Cys Gln Gln Glu Ala Asn Met Asp Arg Pro Ile Ala Gly Tyr
 130 135 140
 Ala Asn Leu Cys Pro Asn Met Ile Ser Thr Gln Pro Gln Glu Phe Val
 145 150 155 160
 Gly Met Leu Ser Thr Val Lys His Glu Val Ile His Ala Leu Gly Phe
 165 170 175
 Ser Ala Gly Leu Phe Ala Phe Tyr His Asp Lys Asp Gly Asn Pro Leu
 180 185 190
 Thr Ser Arg Phe Ala Asp Gly Leu Pro Pro Phe Asn Tyr Ser Leu Gly
 195 200 205
 Leu Tyr Gln Trp Ser Asp Lys Val Val Arg Lys Val Xaa Arg Leu Trp
 210 215 220
 Asp Val Arg Asp Asn Lys Ile Val Arg His Thr Val Tyr Leu Leu Val
 225 230 235 240
 Thr Pro Arg Val Val Glu Glu Ala Arg Lys His Phe Asp Cys Pro Val
 245 250 255
 Leu Glu Gly Met Glu Leu Glu Asn Gln Gly Gly Val Gly Thr Glu Leu
 260 265 270
 Asn His Trp Glu Lys Arg Leu Leu Glu Asn Glu Ala Met Thr Gly Ser
 275 280 285
 His Thr Gln Asn Arg Val Leu Ser Arg Ile Thr Leu Ala Leu Met Glu
 290 295 300

Asp Thr Gly Trp Tyr Lys Ala Asn Tyr Ser Met Ala Glu Lys Leu Asp
 305 310 315 320
 Trp Gly Arg Gly Met Gly Cys Asp Phe Val Arg Lys Ser Cys Lys Phe
 325 330 335
 Trp Ile Asp Gln Gln Arg Gln Lys Arg Gln Met Leu Ser Pro Tyr Cys
 340 345 350
 Asp Thr Leu Arg Ser Asn Pro Leu Gln Leu Thr Cys Arg Gln Asp Gln
 355 360 365
 Arg Ala Val Ala Val Cys Asn Leu Gln Lys Phe Pro Lys Pro Leu Pro
 370 375 380
 Gln Glu Tyr Gln Tyr Phe Asp Glu Leu Ser Gly Ile Pro Ala Glu Asp
 385 390 395 400
 Leu Pro Tyr Tyr Gly Gly Ser Val Glu Ile Ala Asp Tyr Xaa Pro Phe
 405 410 415
 Ser Gln Glu Phe Ser Trp His Leu Ser Gly Glu Tyr Gln Arg Ser Ser
 420 425 430
 Asp Cys Arg Ile Leu Glu Asn Gln Pro Glu Ile Phe Lys Asn Tyr Gly
 435 440 445
 Ala Glu Lys Tyr Gly Pro His Ser Val Cys Leu Ile Gln Lys Ser Ala
 450 455 460
 Phe Val Met Glu Lys Cys Glu Arg Lys Leu Ser Tyr Pro Asp Trp Gly
 465 470 475 480
 Ser Gly Cys Tyr Gln Val Ser Cys Ser Pro Gln Gly Leu Lys Val Trp
 485 490 495
 Val Gln Asp Thr Ser Tyr Leu Cys Ser Arg Ala Gly Gln Val Leu Pro
 500 505 510
 Val Ser Ile Gln Met Asn Gly Trp Ile His Asp Gly Asn Leu Leu Cys
 515 520 525
 Pro Ser Cys Trp Asp Phe Cys Glu Leu Cys Pro Pro Glu Thr Asp Pro
 530 535 540
 Pro Ala Thr Asn Leu Thr Arg Ala Leu Pro Leu Asp Leu Cys Ser Cys
 545 550 555 560
 Ser Ser

<210> 145

<211> 47

<212> PRT

<213> Homo sapiens

<220>
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 <222> (2)
 <223> Xaa equals any of the naturally occurring L-amino acids

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 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (18)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 145
 Glu Xaa Leu Leu Pro Glu Lys Lys Asn Leu Val Lys Asn Lys Leu Leu
 1 5 10 15
 Xaa Xaa Ala Ile Ser Tyr Leu Glu Lys Thr Phe Gln Val Arg Arg Pro
 20 25 30
 Ala Gly Thr Ile Leu Leu Ser Arg Gln Cys Ala Thr Asn Gln Tyr
 35 40 45

<210> 146
 <211> 45
 <212> PRT
 <213> Homo sapiens

<400> 146
 Leu Arg Lys Glu Asn Asp Pro His Arg Tyr Cys Thr Gly Glu Cys Ala
 1 5 10 15
 Ala His Thr Lys Cys Gly Pro Val Ile Val Pro Glu Glu His Leu Gln
 20 25 30
 Gln Cys Arg Val Tyr Arg Gly Gly Lys Trp Pro His Gly
 35 40 45

<210> 147
 <211> 45
 <212> PRT
 <213> Homo sapiens

<400> 147
 Ala Val Gly Val Pro Asp Gln Glu Gly Ile Ser Asp Ala Asp Phe Val
 1 5 10 15
 Leu Tyr Val Gly Ala Leu Ala Thr Glu Arg Cys Ser His Glu Asn Ile
 20 25 30
 Ile Ser Tyr Ala Ala Tyr Cys Gln Gln Glu Ala Asn Met
 35 40 45

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<210> 148
<211> 46
<212> PRT
<213> Homo sapiens

<400> 148
Asp Arg Pro Ile Ala Gly Tyr Ala Asn Leu Cys Pro Asn Met Ile Ser
1 5 10 15
Thr Gln Pro Gln Glu Phe Val Gly Met Leu Ser Thr Val Lys His Glu
20 25 30
Val Ile His Ala Leu Gly Phe Ser Ala Gly Leu Phe Ala Phe
35 40 45

<210> 149
<211> 45
<212> PRT
<213> Homo sapiens

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<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 149
Tyr His Asp Lys Asp Gly Asn Pro Leu Thr Ser Arg Phe Ala Asp Gly
1 5 10 15
Leu Pro Pro Phe Asn Tyr Ser Leu Gly Leu Tyr Gln Trp Ser Asp Lys
20 25 30
Val Val Arg Lys Val Xaa Arg Leu Trp Asp Val Arg Asp
35 40 45

<210> 150
<211> 46
<212> PRT
<213> Homo sapiens

<400> 150
Asn Lys Ile Val Arg His Thr Val Tyr Leu Leu Val Thr Pro Arg Val
1 5 10 15
Val Glu Glu Ala Arg Lys His Phe Asp Cys Pro Val Leu Glu Gly Met
20 25 30
Glu Leu Glu Asn Gln Gly Gly Val Gly Thr Glu Leu Asn His
35 40 45

<210> 151
<211> 45
<212> PRT
<213> Homo sapiens

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<400> 151

Trp Glu Lys Arg Leu Leu Glu Asn Glu Ala Met Thr Gly Ser His Thr
1 5 10 15

Gln Asn Arg Val Leu Ser Arg Ile Thr Leu Ala Leu Met Glu Asp Thr
20 25 30

Gly Trp Tyr Lys Ala Asn Tyr Ser Met Ala Glu Lys Leu
35 40 45

<210> 152

<211> 45

<212> PRT

<213> Homo sapiens

<400> 152

Asp Trp Gly Arg Gly Met Gly Cys Asp Phe Val Arg Lys Ser Cys Lys
1 5 10 15

Phe Trp Ile Asp Gln Gln Arg Gln Lys Arg Gln Met Leu Ser Pro Tyr
20 25 30

Cys Asp Thr Leu Arg Ser Asn Pro Leu Gln Leu Thr Cys
35 40 45

<210> 153

<211> 47

<212> PRT

<213> Homo sapiens

<400> 153

Arg Gln Asp Gln Arg Ala Val Ala Val Cys Asn Leu Gln Lys Phe Pro
1 5 10 15

Lys Pro Leu Pro Gln Glu Tyr Gln Tyr Phe Asp Glu Leu Ser Gly Ile
20 25 30

Pro Ala Glu Asp Leu Pro Tyr Tyr Gly Gly Ser Val Glu Ile Ala
35 40 45

<210> 154

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 154

Asp Tyr Xaa Pro Phe Ser Gln Glu Phe Ser Trp His Leu Ser Gly Glu
1 5 10 15

Tyr Gln Arg Ser Ser Asp Cys Arg Ile Leu Glu Asn Gln Pro Glu Ile

20 25 30
 Phe Lys Asn Tyr Gly Ala Glu Lys Tyr Gly Pro His Ser Val Cys Leu
 35 40 45

<210> 155
 <211> 46
 <212> PRT
 <213> Homo sapiens

<400> 155
 Ile Gln Lys Ser Ala Phe Val Met Glu Lys Cys Glu Arg Lys Leu Ser
 1 5 10 15

Tyr Pro Asp Trp Gly Ser Gly Cys Tyr Gln Val Ser Cys Ser Pro Gln
 20 25 30

Gly Leu Lys Val Trp Val Gln Asp Thr Ser Tyr Leu Cys Ser
 35 40 45

<210> 156
 <211> 57
 <212> PRT
 <213> Homo sapiens

<400> 156
 Arg Ala Gly Gln Val Leu Pro Val Ser Ile Gln Met Asn Gly Trp Ile
 1 5 10 15

His Asp Gly Asn Leu Leu Cys Pro Ser Cys Trp Asp Phe Cys Glu Leu
 20 25 30

Cys Pro Pro Glu Thr Asp Pro Pro Ala Thr Asn Leu Thr Arg Ala Leu
 35 40 45

Pro Leu Asp Leu Cys Ser Cys Ser Ser
 50 55

<210> 157
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 157
 Ile Lys Glu Lys Leu His Val His Gly
 1 5

<210> 158
 <211> 9
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 <213> Homo sapiens

<400> 158

Gly Phe Gly Val Tyr Ile Leu Tyr Ala
1 5

<210> 159

<211> 17

<212> PRT

<213> Homo sapiens

<400> 159

Lys Pro Ser Gly Thr Val Tyr Thr Leu Phe Ser Leu Asn Ser Gly Thr
1 5 10 15

Leu

<210> 160

<211> 19

<212> PRT

<213> Homo sapiens

<400> 160

Ala Asp Leu Thr Ala Val Cys Ser Ala Trp Lys Pro Gly Ala Lys Pro
1 5 10 15

Val Gly Leu

<210> 161

<211> 19

<212> PRT

<213> Homo sapiens

<400> 161

Ala Asp Leu Thr Ala Val Cys Ser Ala Trp Lys Pro Gly Ala Lys Pro
1 5 10 15

Val Gly Leu

<210> 162

<211> 60

<212> PRT

<213> Homo sapiens

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<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 162

Thr Thr Trp Ala Thr Ser Ser Val Val Ala Arg Xaa Thr His His Leu
1 5 10 15

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Phe Pro Pro His Ser Gly Ile Ser Val Asn Ile Gln Asp Leu Ala Pro
20 25 30

Ser Cys Ala Gly Phe Leu Phe Gly Val Ala Asn Thr Ala Gly Ala Leu
35 40 45

Ala Gly Val Val Gly Val Cys Leu Gly Gly Tyr Leu
50 55 60

<210> 163

<211> 27

<212> PRT

<213> Homo sapiens

<400> 163

Asp Ser Pro Leu Thr Val Leu Pro Glu Asp Gly Tyr Gly Ser Asp Ser
1 5 10 15

His Leu Ser Ser Gln Val Val Arg Gly Pro Thr
20 25

<210> 164

<211> 23

<212> PRT

<213> Homo sapiens

<400> 164

Val Glu Ala Ile Phe Ser Glu Leu Val Ile Val Leu Asn Lys Met Ser
1 5 10 15

His Cys Val Leu Ser Gly Thr
20

<210> 165

<211> 26

<212> PRT

<213> Homo sapiens

<400> 165


Lys Pro Thr Lys Met Pro Leu Leu Trp Val Trp Ala Leu Ile Ala Ala
1 5 10 15

Val Ser Gln Pro Glu Leu Trp Tyr Arg Glu
20 25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/02293

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : C07H 21/00; C12N 1/21, 5/10, 15/12, 15/63, 15/70, 15/74, 15/79; US CL : 435/252.3, 320.1, 325, 440; 536/23.1, 23.5 According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/252.3, 320.1, 325, 440; 536/23.1, 23.5 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) GENBANK, EMBL search terms: SEQ ID NO: 11-20,																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT																				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA552323, NCI-CGAP 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), tumor gene index', entire record, 05 September 1997.	1, 7-10																		
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA639694, NCI-CGAP 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), tumor gene index', entire record, 23 October 1997.	1, 7-10																		
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA338949, ADAMS et al. 'Initial assessment of human gene diversity and expression patterns based upon 83 million nucleotides of cDNA sequence', entire record, 21 April 1997.	1, 7-10																		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"> <tr> <td>* Special categories of cited documents:</td> <td>*T</td> <td>later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>*A document defining the general state of the art which is not considered to be of particular relevance</td> <td>*X</td> <td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>*B earlier document published on or after the international filing date</td> <td>*Y</td> <td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>*A</td> <td>document member of the same patent family</td> </tr> <tr> <td>*O document referring to an oral disclosure, use, exhibition or other means</td> <td></td> <td></td> </tr> <tr> <td>*P document published prior to the international filing date but later than the priority date claimed</td> <td></td> <td></td> </tr> </table>			* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*B earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A	document member of the same patent family	*O document referring to an oral disclosure, use, exhibition or other means			*P document published prior to the international filing date but later than the priority date claimed		
* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention																		
*A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																		
*B earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																		
*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A	document member of the same patent family																		
*O document referring to an oral disclosure, use, exhibition or other means																				
*P document published prior to the international filing date but later than the priority date claimed																				
Date of the actual completion of the international search		Date of mailing of the international search report																		
27 APRIL 1999		14 MAY 1999																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer SCOTT D. PRIEBE  Telephone No. (703) 308-0196																		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/02293

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA442570, HILLIER et al. 'WashU-Merck EST Project 1997', entire record, 02 June 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. N32595, HILLIER et al. 'WashU-Merck EST Project', entire record, 10 January 1996.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. N71600, HILLIER et al. 'WashU-Merck EST Project', entire record, 02 April 1996.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA642074, NCI-CGAP 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), tumor gene index', entire record, 27 October 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA555076, NCI-CGAP 'National Cancer Institute, Cancer Genome Anatomy Project (CGAP), tumor gene index', entire record, 05 September 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA442426, HILLIER et al. 'WashU-Merck EST Project 1997', entire record, 02 June 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), NO. AA463820, HILLIER et al. 'WashU-Merck EST Project 1997', entire record, 10 June 1997.	1, 7-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/02293

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10, 21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

- Groups I-XI, claim(s) 1-10 and 21, drawn to a polynucleotide, vector comprising same, first claimed method of use, i.e. using polynucleotide to make a cell, and the cell made by the process. Claims 1-10 and 21 recite 49 independent polynucleotides (SEQ ID NO: 11-59 or encoding SEQ ID NO: 60-108). Group I consists of the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 60-69). Each of groups II-XI consists of up to four of the remaining 39 polynucleotides, in order.
- Groups XII-LX, claim(s) 11, 12, 14-16 and 17 (first part), drawn to a polypeptide, a method of making the polypeptide and first claimed method of use, i.e. in treatment. These claims recite 49 independent polypeptides, each of groups XII-LX consists of a single polypeptide as set forth in SEQ ID NOs 60-108, respectively.
- Groups LXI-CIX, claim(s) 13 and 19, drawn to an antibody to a polypeptide and the first claimed method of using same. These claims recite 49 independent antibodies to 49 independent polypeptides, each of groups LXI-CIX consists an antibody against a single polypeptide as set forth in SEQ ID NOs 60-108, respectively.
- Groups CX-CXX, claim(s) 17(second part), drawn to an additional method of using a polynucleotide. Group CCLVI consists of methods reciting the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 60-69). Each of groups CCLVII-CCLXXXII pertains to up to four of the remaining 39 polynucleotides, in order.
- Groups CXXI-CXXXI, claim(s) 18, drawn to a second additional method of using a polynucleotide. Group CXXI consists of methods reciting the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 60-108). Each of groups CXXII-CXXXI pertains to up to four of the remaining 39 polynucleotides, in order.
- Groups CXXXII-CLXXX, claim(s) 20 and 23, drawn to an additional method of using the polypeptide and product made. These claims recite 49 independent methods of using 49 independent polypeptides as set forth in SEQ ID NOs 60-108, respectively.
- Groups CLXXXI-CXCI, claim 22, drawn to a third additional method of using a polynucleotide. Group CLXXXI consists of methods reciting the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 60-69). Each of groups CLXXXII-CXCI pertains to up to four of the remaining 39 polynucleotides, in order.

The inventions listed as Groups I-CXLI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Each of the corresponding polynucleotides, polypeptides and antibodies are independent products, with different uses and being structurally, biochemically and biologically different products. Additional or alternate methods of use are claimed for individual polynucleotides and polypeptides. 37 CFR 1.475(b) does not provide for unity of invention of more than 1 product or more than one method of using a product as a combination of invention having unity of invention. However, with respect to groups drawn to independent polynucleotides or alternate methods of using same recited in the alternative, in accordance with 1192 O.G. 68 (19 November 1966) applicant is entitled to an initial search of inventions pertaining to the first ten independent polynucleotides recited, and may elect to pay an additional fee for each search of up to four additional independent polynucleotides. For additional method of using each of the independent polynucleotides, applicant may further elect to pay an additional fee for an additional search involving the first ten polynucleotides and each additional search involving up to four additional polynucleotides. With respect to groups pertaining to independent polypeptides or antibodies to the independent polypeptides, each product or method of use is an additional invention. An additional fee must be paid for search of each additional invention relating to polypeptides or antibodies against same. With respect to the relationship between the claimed polynucleotides and the claimed polypeptides, there is no one-to-one correspondence, i.e. no corresponding scope, between claims drawn to polynucleotides and their use and those drawn to polypeptides, antibodies and their use. Consequently, there is no special technical feature linking the polynucleotides and the polypeptides or antibodies claimed.